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(54) Title: NOVEL NUCLEIC ACIDS AND POLYPEPTIDES AND METHODS OF USE THEREOF

(57) Abstract: Disclosed are novel polypeptides and nucleic acids encoding same. Also disclosed are vectors, host cells, antibodies and recombinant methods for producing the polypeptides and polynucleotides, as well as methods for using same.

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NOVEL NUCLEIC ACIDS AND POLYPEPTIDES AND METHODS OF USE THEREOF

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FIELD OF THE INVENTION

The present invention relates to polynucleotides and the polypeptides encoded by such polynucleotides, as well as vectors, host cells, antibodies and recombinant methods for producing the polypeptides and polynucleotides, as well as methods for using the same.

10

BACKGROUND OF THE INVENTION

The invention generally relates to nucleic acids and polypeptides encoded therefrom. More specifically, the invention relates to nucleic acids encoding cytoplasmic, nuclear, membrane bound, and secreted polypeptides, as well as vectors, host cells, antibodies, and recombinant methods for producing these nucleic acids and polypeptides.

15

SUMMARY OF THE INVENTION

The invention is based in part upon the discovery of nucleic acid sequences encoding novel polypeptides. The novel nucleic acids and polypeptides are referred to herein as NOVX, or NOV1, NOV2, NOV3, NOV4, NOV5, NOV6, NOV7, NOV8, NOV9, NOV10, NOV11 and NOV12 nucleic acids and polypeptides. These nucleic acids and polypeptides, as well as derivatives, homologs, analogs and fragments thereof, will hereinafter be collectively designated as "NOVX" nucleic acid or polypeptide sequences.

20

In one aspect, the invention provides an isolated NOVX nucleic acid molecule encoding a NOVX polypeptide that includes a nucleic acid sequence that has identity to the nucleic acids disclosed in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37. In some embodiments, the NOVX nucleic acid molecule will hybridize under stringent conditions to a nucleic acid sequence complementary to a nucleic acid molecule that includes a protein-coding sequence of a NOVX nucleic acid sequence. The invention also

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includes an isolated nucleic acid that encodes a NOVX polypeptide, or a fragment, homolog, analog or derivative thereof. For example, the nucleic acid can encode a polypeptide at least 80% identical to a polypeptide comprising the amino acid sequences of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, and 38. The nucleic acid can be, for example, a genomic DNA fragment or a cDNA molecule that includes the nucleic acid sequence of any of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37.

Also included in the invention is an oligonucleotide, *e.g.*, an oligonucleotide which includes at least 6 contiguous nucleotides of a NOVX nucleic acid (*e.g.*, SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37) or a complement of said oligonucleotide. Also included in the invention are substantially purified NOVX polypeptides (SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, and 38). In certain embodiments, the NOVX polypeptides include an amino acid sequence that is substantially identical to the amino acid sequence of a human NOVX polypeptide.

The invention also features antibodies that immunoselectively bind to NOVX polypeptides, or fragments, homologs, analogs or derivatives thereof.

In another aspect, the invention includes pharmaceutical compositions that include therapeutically- or prophylactically-effective amounts of a therapeutic and a pharmaceutically-acceptable carrier. The therapeutic can be, *e.g.*, a NOVX nucleic acid, a NOVX polypeptide, or an antibody specific for a NOVX polypeptide. In a further aspect, the invention includes, in one or more containers, a therapeutically- or prophylactically-effective amount of this pharmaceutical composition.

In a further aspect, the invention includes a method of producing a polypeptide by culturing a cell that includes a NOVX nucleic acid, under conditions allowing for expression of the NOVX polypeptide encoded by the DNA. If desired, the NOVX polypeptide can then be recovered.

In another aspect, the invention includes a method of detecting the presence of a NOVX polypeptide in a sample. In the method, a sample is contacted with a compound that selectively binds to the polypeptide under conditions allowing for formation of a complex between the polypeptide and the compound. The complex is detected, if present, thereby identifying the NOVX polypeptide within the sample.

The invention also includes methods to identify specific cell or tissue types based on their expression of a NOVX.

Also included in the invention is a method of detecting the presence of a NOVX nucleic acid molecule in a sample by contacting the sample with a NOVX nucleic acid probe or primer, and detecting whether the nucleic acid probe or primer bound to a NOVX nucleic acid molecule in the sample.

In a further aspect, the invention provides a method for modulating the activity of a NOVX polypeptide by contacting a cell sample that includes the NOVX polypeptide with a compound that binds to the NOVX polypeptide in an amount sufficient to modulate the activity of said polypeptide. The compound can be, *e.g.*, a small molecule, such as a nucleic acid, peptide, polypeptide, peptidomimetic, carbohydrate, lipid or other organic (carbon containing) or inorganic molecule, as further described herein.

Also within the scope of the invention is the use of a therapeutic in the manufacture of a medicament for treating or preventing disorders or syndromes including, *e.g.*, Cancer, Hodgkin disease, Von Hippel-Lindau (VHL) syndrome, hypercalcaemia, Endometriosis, Crohn's Disease, Xerostomia, Inflammatory bowel disease, Diverticular disease, fertility, Infertility, CNS disorders, osteoporosis, atherosclerosis, hypertension, congenital heart defects, aortic stenosis, valve diseases, tuberous sclerosis, scleroderma, Hemophilia, obesity, Diabetes, Pancreatitis, transplantation recovery, Autoimmune disease, asthma, arthritis, Immunodeficiencies, Graft vesus host, Alzheimer's disease, Stroke, Parkinson's disease, Huntington's disease, Cerebral palsy, Epilepsy, Multiple sclerosis, Ataxia-telangiectasia, Behavioral disorders, Addiction, Anxiety, Pain, Muscular dystrophy, and/or other pathologies and disorders of the like.

The therapeutic can be, *e.g.*, a NOVX nucleic acid, a NOVX polypeptide, or a NOVX-specific antibody, or biologically-active derivatives or fragments thereof.

For example, the compositions of the present invention will have efficacy for treatment of patients suffering from the diseases and disorders disclosed above and/or other pathologies and disorders of the like. The polypeptides can be used as immunogens to produce antibodies specific for the invention, and as vaccines. They can also be used to screen for potential agonist and antagonist compounds. For example, a cDNA encoding NOVX may be useful in gene therapy, and NOVX may be useful when administered to a subject in need thereof. By way of non-limiting example, the compositions of the present invention will have efficacy for treatment of

patients suffering from the diseases and disorders disclosed above and/or other pathologies and disorders of the like.

5 The invention further includes a method for screening for a modulator of disorders or syndromes including, *e.g.*, the diseases and disorders disclosed above and/or other pathologies and disorders of the like. The method includes contacting a test compound with a NOVX polypeptide and determining if the test compound binds to said NOVX polypeptide. Binding of the test compound to the NOVX polypeptide indicates the test compound is a modulator of activity, or of latency or predisposition to the aforementioned disorders or syndromes.

10 Also within the scope of the invention is a method for screening for a modulator of activity, or of latency or predisposition to disorders or syndromes including, *e.g.*, the diseases and disorders disclosed above and/or other pathologies and disorders of the like by administering a test compound to a test animal at increased risk for the aforementioned disorders or syndromes. The test animal expresses a recombinant polypeptide encoded by a NOVX nucleic acid. Expression or activity of NOVX polypeptide is then measured in the test animal, as is expression
15 or activity of the protein in a control animal which recombinantly-expresses NOVX polypeptide and is not at increased risk for the disorder or syndrome. Next, the expression of NOVX polypeptide in both the test animal and the control animal is compared. A change in the activity of NOVX polypeptide in the test animal relative to the control animal indicates the test compound is a modulator of latency of the disorder or syndrome.

20 In yet another aspect, the invention includes a method for determining the presence of or predisposition to a disease associated with altered levels of a NOVX polypeptide, a NOVX nucleic acid, or both, in a subject (*e.g.*, a human subject). The method includes measuring the amount of the NOVX polypeptide in a test sample from the subject and comparing the amount of the polypeptide in the test sample to the amount of the NOVX polypeptide present in a control
25 sample. An alteration in the level of the NOVX polypeptide in the test sample as compared to the control sample indicates the presence of or predisposition to a disease in the subject. Preferably, the predisposition includes, *e.g.*, the diseases and disorders disclosed above and/or other pathologies and disorders of the like. Also, the expression levels of the new polypeptides of the invention can be used in a method to screen for various cancers as well as to determine the stage
30 of cancers.

In a further aspect, the invention includes a method of treating or preventing a pathological condition associated with a disorder in a mammal by administering to the subject a NOVX polypeptide, a NOVX nucleic acid, or a NOVX-specific antibody to a subject (*e.g.*, a human subject), in an amount sufficient to alleviate or prevent the pathological condition. In preferred
5 embodiments, the disorder, includes, *e.g.*, the diseases and disorders disclosed above and/or other pathologies and disorders of the like.

In yet another aspect, the invention can be used in a method to identity the cellular receptors and downstream effectors of the invention by any one of a number of techniques commonly employed in the art. These include but are not limited to the two-hybrid system,
10 affinity purification, co-precipitation with antibodies or other specific-interacting molecules.

NOVX nucleic acids and polypeptides are further useful in the generation of antibodies that bind immuno-specifically to the novel NOVX substances for use in therapeutic or diagnostic methods. These NOVX antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies"
15 section below. The disclosed NOVX proteins have multiple hydrophilic regions, each of which can be used as an immunogen. These NOVX proteins can be used in assay systems for functional analysis of various human disorders, which will help in understanding of pathology of the disease and development of new drug targets for various disorders.

The NOVX nucleic acids and proteins identified here may be useful in potential
20 therapeutic applications implicated in (but not limited to) various pathologies and disorders as indicated below. The potential therapeutic applications for this invention include, but are not limited to: protein therapeutic, small molecule drug target, antibody target (therapeutic, diagnostic, drug targeting/cytotoxic antibody), diagnostic and/or prognostic marker, gene therapy (gene delivery/gene ablation), research tools, tissue regeneration in vivo and in vitro of all tissues
25 and cell types composing (but not limited to) those defined here.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are
30 described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In the case of conflict, the present

specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

Other features and advantages of the invention will be apparent from the following detailed description and claims.

5

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides novel nucleotides and polypeptides encoded thereby. Included in the invention are the novel nucleic acid sequences and their encoded polypeptides. The sequences are collectively referred to herein as "NOVX nucleic acids" or "NOVX polynucleotides" and the corresponding encoded polypeptides are referred to as "NOVX polypeptides" or "NOVX proteins." Unless indicated otherwise, "NOVX" is meant to refer to any of the novel sequences disclosed herein. Table A provides a summary of the NOVX nucleic acids and their encoded polypeptides.

TABLE A. Sequences and Corresponding SEQ ID Numbers

NOVX No.	Internal Acc. No.	Homology	Nucleic Acid SEQ ID NO.	Polypeptide SEQ ID NO.
1a	CG-AC084364.5 / AC084364.5	Stabilin	1	2
1b	CG50736-10/11400078	Stabilin	3	4
1c	CG50736-09	CD44-like Precursor/ Fascilin domain	210	211
2a	CG142106342 / CG50646-04	Polydom	5	6
2b	CG50646-05	Polydom	7	8
3a	CG50273-01	Transmembrane Protein	9	10
3b	CG50273-02	Transmembrane IIIb Protein	11	12
4	CG50289-01	Serine Protease	13	14
5a	CG50353-01	Wnt 7a Protein	15	16
5b	169475673 (insert assembly of NOV5a)	Wnt 7a protein	17	18
6a	CG50221-01	Apical Endosomal	19	20

		Glycoprotein		
6b	174308633 (insert assembly of NOV6a)	Apical Endosomal Glycoprotein	N/A	N/A
7a	CG50367-01	ADAM13	21	22
7b	CG50367-02	ADAM13	23	24
7c	CG50367-03	ADAM13	25	26
8	CG50321-01	Leucine Rich Containing F Box	27	28
9	CG55902-01	Steroid Binding	29	30
10a	CG50307-01	Steroid Dehydrogenase	31	32
10b	CG50307-02	Steroid Dehydrogenase	33	34
11	CG50311-01	Myosin Heavy Chain	35	36
12a	CG50323-01	Pancreatitis-Associated Protein (PAP)	37	38
12b	169475472 (insert assembly of NOV12a)	PAP	N/A	N/A
12c	169475476 (Insert assembly of NOV12a)	PAP	N/A	N/A

NOVX nucleic acids and their encoded polypeptides are useful in a variety of applications and contexts. The various NOVX nucleic acids and polypeptides according to the invention are useful as novel members of the protein families according to the presence of domains and sequence relatedness to previously described proteins. Additionally, NOVX nucleic acids and polypeptides can also be used to identify proteins that are members of the family to which the NOVX polypeptides belong.

The present invention is based in part on nucleic acids encoding proteins that are novel members of the following protein families: Stabilin/Fascilin/CD-44 precursor FELL-like, Polydom, Transmembrane/IIIb, Serine Protease, Wnt-7a, Apical endosomal glycoprotein, ADAM13, Leucine-rich containing F-Box, Pancreatitis-Associated, Steroid Binding, Steroid dehydrogenase, and Myosin Heavy-chain-like proteins. More particularly, the invention relates to nucleic acids encoding novel polypeptides, as well as vectors, host cells, antibodies, and recombinant methods for producing these nucleic acids and polypeptides.

NOV1 is homologous to the Stabilin family of proteins. Thus, the NOV1 nucleic acids, polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example, cancer, particularly mechanisms of angiogenesis, inflammation, CNS disorders, metabolic disorders including obesity and diabetes and/or other pathologies/disorders.

Fascilin domain-containing proteins have been shown to be important for cell adhesion, which impacts a variety of diseases including cancer, inflammation, obesity and CNS disorders. Stabilin-1 is an endothelial-macrophage member of the fascilin domain containing protein family associated with angiogenesis.

NOV2 is homologous to the Polydom family of proteins. Thus NOV2 nucleic acids, polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example, inflammatory diseases, disorders of coagulation, cancer, obesity, diabetes, asthma, arthritis, osteoporosis, cardiovascular disease and/or other pathologies/disorders.

The mouse polydom protein appears to be important for the regulation of hematopoiesis and may play a role in cell adhesion or in the immune system. Domains within this protein and the human ortholog have been shown to be important in coagulation, growth, cell division, and other important cellular processes.

NOV3 is homologous to a transmembrane/IIIb protein. Thus, the NOV3 nucleic acids and polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example, cancer, trauma, regeneration (in vitro and in vivo), viral/bacterial/parasitic infections, neuroprotection, Von Hippel-Lindau (VHL) syndrome, Alzheimer's disease, stroke, tuberous sclerosis, hypercalcaemia, Parkinson's disease, Huntington's disease, cerebral palsy, epilepsy, Lesch-Nyhan syndrome, multiple sclerosis, ataxia-telangiectasia, leukodystrophies, behavioral disorders, addiction, anxiety, pain, and/or other pathologies/disorders.

The human transmembrane protein described herein has homology to a mouse protein that causes growth inhibition of *E. coli* when expressed exogenously. Therefore, the disclosed transmembrane/IIIb protein of this invention will fulfill a similar function in humans.

NOV4 is homologous to a Serine protease family of proteins. Thus, NOV4 nucleic acids, polypeptides, antibodies and related compounds according to the invention will be useful in

therapeutic and diagnostic applications implicated in, for example, cancer, trauma, regeneration (in vitro and in vivo), viral/bacterial/parasitic infections, infertility, and/or other pathologies/disorders.

Proteolytic enzymes that exploit serine in their catalytic activity are ubiquitous, being
5 found in viruses, bacteria and eukaryotes. They include a wide range of peptidase activity, including exopeptidase, endopeptidase, oligopeptidase and omega-peptidase activity. Over 20 families of serine protease have been identified and although they have different evolutionary origins, there are similarities in the reaction mechanisms of several peptidases. Chymotrypsin, subtilisin and carboxypeptidase C clans have a catalytic triad of serine, aspartate and histidine in
10 common: serine acts as a nucleophile, aspartate as an electrophile, and histidine as a base. The geometric orientations of the catalytic residues are similar between families, despite different protein folds. The trypsin family is almost totally confined to animals, although trypsin-like enzymes are found in actinomycetes of the genera *Streptomyces* and *Saccharopolyspora*, and in the fungus *Fusarium oxysporum*. The enzymes are inherently secreted, being synthesised with a
15 signal peptide that targets them to the secretory pathway. Animal enzymes are either secreted directly, packaged into vesicles for regulated secretion, or are retained in leukocyte granules.

The NOV4 nucleic acid and polypeptide described in this application has a structure similar to TESP-1 and TESP-2; serine proteases isolated from mouse sperm acrosome. These
enzymes are secreted as zymogens and released by the acrosome reaction induced by the calcium
20 ionophore; A23187. These may play a role in fertilization and/or processing of other proteins during fertilization.

NOV5 is homologous to the Wnt-7a protein family. Thus NOV5 nucleic acids, polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example, atherosclerosis, aneurysm,
25 hypertension, fibromuscular dysplasia, stroke, scleroderma, obesity, transplantation disorders, myocardial infarction, embolism, cardiovascular disorders, bypass surgery, endometriosis, infertility, polycystic ovary syndrome, Von Hippel-Lindau (VHL) syndrome, Alzheimer's disease, tuberous sclerosis, hypercalcaemia, Parkinson's disease, Huntington's disease, cerebral palsy, epilepsy, Lesch-Nyhan syndrome, multiple sclerosis, ataxia-telangiectasia, leukodystrophies,
30 behavioral disorders, addiction, anxiety, pain, neurodegeneration, cancer, psoriasis, actinic

keratosis, acne, hair growth/loss, alopecia, pigmentation disorders, endocrine disorders, pancreatitis, diabetes, and/or other pathologies/disorders.

Wnt proteins constitute a large family of molecules involved in cell proliferation, cell differentiation and embryonic patterning. They are known to interact with the Frizzled family of receptors to activate two main intracellular signaling pathways regulating intracellular calcium levels and gene transcription. Early studies on Wnts implicated them in cell proliferation and tumorigenesis, which have been borne out by recent work using transgenic and null mutant mice. Wnts are involved in processes involved in mammary gland development and cancer. Recent studies have demonstrated that these molecules are critical to organogenesis of several systems, such as the kidney and brain. Wnts regulate the early development, i.e. neural induction, and their role persists in later stages of development as well as in the mature organ. An example of this is seen in the brain, where the loss of certain Wnts leads to the absence of critical regions of the brain, e.g. the hippocampus, involved in learning and memory, or the cerebellum, involved in motor function. Wnts have also been implicated in the genesis of degenerative diseases such as Alzheimer's disease.

The NOV5 nucleic acid and polypeptide of the invention has a high degree of similarity to Wnt-7a. Wnt-7a is known to be involved in the development of the limbs, the female reproductive system and the brain. Mutations in Wnt-7a lead to limb patterning defects along with sterility in both males and females. Ectopic expression of this protein leads to inhibition of chondrogenesis. This novel gene may therefore have therapeutic importance in several kinds of developmental defects and cancer, among other pathologies/disorders described above.

NOV6 is homologous to the Apical endosomal glycoprotein family of proteins. Thus NOV6 nucleic acids, polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example, endometriosis, fertility, and/or other pathologies/disorders.

After endocytosis from the plasma membrane, internalized receptors and ligands are delivered to endosomes. The endosomal compartment performs a variety of functions, including the sorting of internalized receptors and ligands, and newly synthesized lysosomal membrane proteins and hydrolases. In polarized epithelial cells, the apical endosomal compartment has been implicated in both apical to basolateral and basolateral to apical transepithelial transport.

NOV7 is homologous to members of the A Disintegrin And Metalloprotease (ADAMs) family of proteins, and specifically domain 13 (ADAM13). Thus, the NOV7 nucleic acids, polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example, Xerostomia, Scleroderma, 5 Hypercalceimia, Ulcers, Von Hippel-Lindau (VHL) syndrome, Cirrhosis, Transplantation, Cirrhosis, Inflammatory bowel disease, Diverticular disease, Hirschsprung's disease, Crohn's Disease, Appendicitis, Endometriosis, Fertility, Cardiomyopathy, Atherosclerosis, Hypertension, Congenital heart defects, Aortic stenosis, Atrial septal defect (ASD), Atrioventricular (A-V) canal defect, Ductus arteriosus, Pulmonary stenosis, Subaortic stenosis, Ventricular septal defect 10 (VSD), valve diseases, Tuberous sclerosis, Scleroderma, Obesity, Aneurysm, Fibromuscular dysplasia, Stroke, Bleeding disorders, Hemophilia, hypercoagulation, Idiopathic thrombocytopenic purpura, autoimmune disease, allergies, immunodeficiencies, Graft versus host, Anemia, Ataxia-telangiectasia, Lymphedema, Allergies, Tonsillitis, and/or other pathologies/disorders.

15 The ADAM family includes proteins containing disintegrin-like and metalloprotease-like domains. They are also referred to as MDC (Metalloprotease, Disintegrin, Cysteine-rich) proteins. ADAMs are involved in diverse processes such as development, cell-cell interactions and protein ectodomain shedding. In *Xenopus*, ADAM13 (most closely related to ADAM12) may be involved in neural crest cell adhesion and migration as well as myoblast differentiation. 20 ADAM12/Meltrin α is required for and provokes myogenesis (myoblast fusion).

NOV8 is homologous to the Leucine-rich containing F-Box family of proteins. Since the NOV8 protein of the invention is ubiquitously expressed in many tissues, the NOV8 nucleic acids and polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in the treatment of patients suffering from 25 diseases associated with these tissues, and/or other pathologies/disorders.

F-box proteins are an expanding family of eukaryotic proteins characterized by an approximately 40 amino acid motif, the F box (so named because cyclin F was one of the first proteins in which this motif was identified). Some F-box proteins have been shown to be critical for the controlled degradation of cellular regulatory proteins. In fact, F-box proteins are one of 30 the four subunits of ubiquitin protein ligases called SCFs. The other three subunits are the Skp1 protein; one of the cullin proteins (Cul1 in metazoans and Cdc53 or Cul A in the yeast

Saccharomyces cerevisiae); and the recently identified Roc1 protein (also called Rbx1 or Hrt1). SCF ligases bring ubiquitin conjugating enzymes (either Ubc3 or Ubc4) to substrates that are specifically recruited by the different F-box proteins. The need for high substrate specificity and the large number of known F-box proteins in yeast and worms suggest the existence of a large family of mammalian F-box proteins. There are 26 human F-box proteins. Some of these proteins contain WD-40 domains or leucine-rich repeats; others contain either different protein-protein interaction modules or no recognizable motifs. F-box proteins that contain WD-40 domains Fbws, those containing leucine-rich repeats, Fbls, and the remaining ones Fbxs. The marked differences in F-box gene expression in human tissues suggest their distinct role in ubiquitin-dependent protein degradation.

NOV9 is homologous to a Steroid binding family of proteins. Thus, the NOV9 nucleic acids, polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example, cancer, cataracts, obesity, diabetes, hyperlipidemia, infertility, inflammation, CNS disorders, and/or other pathologies/disorders.

Steroid binding proteins involve reproductive behavior, cell cycle progression and various important physiologic pathologies. Steroid hormones control many normal biological processes but can also cause several disease processes including hormone-dependent cancers of male and female reproductive tissues.

NOV10 is homologous to members of the steroid dehydrogenase family of proteins. Thus, the NOV10 nucleic acids, polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example, cardiomyopathy, atherosclerosis, hypertension, congenital heart defects, aortic stenosis, atrial septal defect (ASD), atrioventricular (A-V) canal defect, ductus arteriosus, pulmonary stenosis, subaortic stenosis, ventricular septal defect (VSD), valve diseases, tuberous sclerosis, scleroderma, obesity, adrenoleukodystrophy, congenital adrenal hyperplasia, diabetes, Von Hippel-Lindau (VHL) syndrome, cirrhosis, pancreatitis, endometriosis, fertility, hemophilia, hypercoagulation, idiopathic thrombocytopenic purpura, autoimmune disease, allergies, immunodeficiencies, transplantation, graft versus host disease, osteoporosis, hypercalcaemia, arthritis, ankylosing spondylitis, scoliosis, muscular dystrophy, Lesch-Nyhan syndrome, myasthenia gravis, Alzheimer's disease, stroke, tuberous sclerosis, hypercalcaemia, Parkinson's

disease, Huntington's disease, cerebral palsy, epilepsy, Lesch-Nyhan syndrome, multiple sclerosis, ataxia-telangiectasia, leukodystrophies, behavioral disorders, addiction, anxiety, pain, neuroprotection, psoriasis, actinic keratosis, acne, hair growth/loss, alopecia, pigmentation disorders, endocrine disorders, and/or other pathologies/disorders.

5 Steroid dehydrogenase enzymes influence mammalian reproduction, hypertension, neoplasia, and Digestion. The three-dimensional structures of steroid dehydrogenase enzymes reveal the position of the catalytic triad, a possible mechanism of keto-hydroxyl interconversion, a molecular mechanism of inhibition, and the basis for selectivity. Glycyrrhizic acid, the active ingredient in licorice, and its metabolite carbenoxolone are potent inhibitors of human 11 beta-
10 hydroxysteroid dehydrogenase and bacterial 3 alpha, 20 beta-hydroxysteroid dehydrogenase (3 alpha, 20 beta-HSD). The three-dimensional structure of the 3 alpha, 20 beta-HSD carbenoxolone complex unequivocally verifies the postulated active site of the enzyme, shows that inhibition is a result of direct competition with the substrate for binding, and provides a plausible model for the mechanism of inhibition of 11 beta-hydroxysteroid dehydrogenase by carbenoxolone. The
15 structure of the ternary complex of human 17 beta-hydroxysteroid dehydrogenase type 1 (17 beta-HSD) with the cofactor NADP⁺ and the antiestrogen equilin reveals the details of binding of an inhibitor in the active site of the enzyme and the possible roles of various amino acids in the catalytic cleft. The short-chain dehydrogenase reductase (SDR) family includes these steroid dehydrogenase enzymes and more than 60 other proteins from human, mammalian, insect, and
20 bacterial sources. Most members of the family contain the tyrosine and lysine of the catalytic triad in a YxxxK sequence. X-ray crystal structures of 13 members of the family have been completed. When the alpha-carbon backbone of the cofactor binding domains of the structures are superimposed, the conserved residues are at the core of the structure and in the cofactor binding domain, but not in the substrate binding pocket.

25 Mutations of steroid dehydrogenases have been found to cause various developmental, reproductive or metabolic disorders. For example, Defects in the conversion of androstenedione to testosterone in the fetal testes by the enzyme 17 beta-hydroxysteroid dehydrogenase (17 beta-HSD) give rise to genetic males with female external genitalia. Missense and splice junction mutations severely compromised the activity of the 17 beta-HSD type 3 isozyme and cause male
30 pseudohermaphroditism. Mutations in the NSDHL gene, encoding a 3beta-hydroxysteroid dehydrogenase, cause CHILD syndrome. Deficient or impaired 11 beta-hydroxy steroid

dehydrogenase in the apparent mineralocorticoid excess syndrome or after licorice ingestion retards the conversion of cortisol to inactive cortisone in the kidney, leading to mineralocorticoid hypertension; this leads to suppression of the renin system and subsequently of aldosterone. In addition, steroid dehydrogenases have been implicated to regulate steroid induced renal reabsorption of sodium. Not only may they control the access of glucocorticoids to MR, but control the access of glucocorticoids to glucocorticoid receptors (GR) as well as access of mineralocorticoids to their own receptors. Finally, steroid dehydrogenases have also been found in neurons and astrocytes, suggesting that these enzymes may be involved in the regulation of brain function. Given their important biological functions, steroid dehydrogenases present excellent small molecule drug targets for therapeutic intervention.

NOV11 is homologous to a Myosin heavy-chain family of proteins. Thus, the NOV11 nucleic acids, polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example, restenosis, neurological, glomerular diseases, and/or other pathologies/disorders.

Myosins are molecular motors that upon interaction with actin filaments convert energy from ATP hydrolysis into mechanical force. Evidence has emerged for the existence of a large, widely expressed and evolutionarily ancient superfamily of myosin genes. In addition to the well-catheterized conventional, filament-forming, two-headed myosin-II of muscle and nonmuscle cells, at least ten additional classes of myosins have been identified. In vertebrates, at least seven of the eleven classes are expressed, and many myosins can be expressed in a single cell type. Distance matrix and maximum parsimony methods have been used to study the evolutionary relationships between members of the myosin superfamily of molecular motors. Amino acid sequences of the conserved core of the motor region were used in the analysis. Myosins can be divided into at least three main classes, with two types of unconventional myosin being no more related to each other than they are to conventional myosin. Myosins have traditionally been classified as conventional or unconventional, with many of the unconventional myosin proteins thought to be distributed in a narrow range of organisms. It has been found that members of all three of these main classes are likely to be present in most (or all) eukaryotes. Three proteins do not cluster within the three main groups and may each represent additional classes. The structure of the trees suggests that these ungrouped proteins and some of the subclasses of the main classes are also likely to be widely distributed, implying that most eukaryotic cells contain many different

myosin proteins. The groupings derived from phylogenetic analysis of myosin head sequences agree strongly with those based on tail structure, developmental expression, and (where available) enzymology, suggesting that specific head sequences have been tightly coupled to specific tail sequences throughout evolution. Analysis of the relationships within each class has interesting implications. For example, smooth muscle myosin and striated muscle myosin seem to have independently evolved from nonmuscle myosin. Furthermore, brush border myosin I, a type of protein initially thought to be specific to specialized metazoan tissues, probably has relatives that are much more broadly distributed. Myosin II, the conventional two-headed myosin that forms bipolar filaments, is directly involved in regulating cytokinesis, cell motility and cell morphology in nonmuscle cells. To understand the mechanisms by which nonmuscle myosin-II regulates these processes, investigators are looking at the regulation of this molecule in vertebrate nonmuscle cells. The identification of multiple isoforms of nonmuscle myosin-II, whose activities and regulation differ from that of smooth muscle myosin-II, suggests that, in addition to regulatory light chain phosphorylation, other regulatory mechanisms control vertebrate nonmuscle myosin-II activity. It has been shown that nonmuscle myosin II, along with other myosins and cytoskeletal proteins, assembles on Golgi membranes. Nonmuscle myosin II associates transiently with membranes of the trans-Golgi network during the budding of a subpopulation of transport vesicles. The exact role of myosin II in vesicular trafficking is not yet understood, but its participation heralds a novel role for actin-based motors in vesicle budding.

In the aortic wall of mammalian species, the maturation phase of smooth muscle cell (SMC) lineage is characterized by two temporally correlated but opposite regulatory processes of gene expression: upregulation of SM type SM2 myosin isoform and down-regulation of brain (myosin heavy chain B)- and platelet (myosin heavy chain A(pla))-type nonmuscle myosins. There is propensity of the immature type SMC population to be activated in experimental models and human vascular diseases that are characterized by proliferation and migration of medial SMCs into the subendothelial space. Neointimal proliferation leading to restenosis frequently develops after coronary angioplasty. This process is associated with a change in vascular smooth-muscle cells from a contractile (quiescent) phenotype to a synthetic or proliferating (activated) one. The expression of the B isoform of nonmuscle myosin heavy chain is increased in some coronary atherosclerotic plaques and that this increase in expression identifies a group of lesions at high risk for restenosis after atherectomy.

The human homologue of the mouse dilute gene combines elements from both nonmuscle myosin type I and nonmuscle myosin type II. Mutations in the mouse dilute gene result not only in the lightening of coat color, but also in the onset of severe neurological defects shortly after birth, indicating that this gene is important in maintaining the normal neuronal function.

5 NOV12 is homologous to a Pancreatitis-associated family of proteins. Thus, the NOV12 nucleic acids, polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example, acute pancreatitis, chronic pancreatitis, and/or other pathologies/disorders.

10 Human Pancreatitis-associated protein (PAP) is a secretory protein that is strongly expressed in the pancreas with pancreatitis, but not in a healthy pancreas. Thus, synthesis increases during inflammation of the pancreas, and a direct relationship between severity of pancreatitis and serum levels of PAP exists. As a result, PAP may be used as a biological marker of acute or chronic pancreatitis.

15 The NOVX nucleic acids and polypeptides can also be used to screen for molecules, which inhibit or enhance NOVX activity or function. Specifically, the nucleic acids and polypeptides according to the invention may be used as targets for the identification of small molecules that modulate or inhibit, e.g., neurogenesis, cell differentiation, cell proliferation, hematopoiesis, wound healing and angiogenesis.

20 Additional utilities for the NOVX nucleic acids and polypeptides according to the invention are disclosed herein.

NOV1

One NOVX protein of the invention, referred to herein as NOV1, includes stabilin-like proteins. The disclosed proteins have been named NOV1a, NOV1b, and NOV1c.

25 Stabilin is a member of the fascilin domain containing protein family, which has been shown to be important for cell adhesion. Although such cell adhesion molecules are typically localized at the neuromuscular junction in *Drosophila*, where they function in the growth and plasticity of the synapse, the protein predicted here is likely to be localized extracellularly in the plasma membrane. Thus, it is likely that the stabilin-like protein of the invention is accessible to a
30 diagnostic probe and for the various therapeutic applications described herein.

The NOV1a protein maps to chromosome 3, whereas the NOV1b protein of the invention maps to chromosome 12. This information was assigned using OMIM, the electronic northern

bioinformatic tool implemented by CuraGen Corporation, public ESTs, public literature references and/or genomic clone homologies.

NOV1a

5 In one embodiment, a NOV1 variant is NOV1a (alternatively referred to herein as CG-AC084364.5), which encodes a novel stabilin-like protein and includes the 8444 nucleotide sequence (SEQ ID NO:1) shown in Table 1A. An open reading frame for the mature protein was identified beginning with an ATG initiation codon at nucleotides 1-3 and ending with a TGA stop codon at nucleotides 8026-8028. Putative untranslated regions downstream from the termination
10 codon are underlined in Table 1A, and the start and stop codons are in bold letters.

Table 1A. NOV1a Nucleotide Sequence (SEQ ID NO:1)

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ATGGGCCTGCGCAGTCTGGGGCTCCTGGCTGTGCTGCCACTTCCTGAGTCAAGCACTGGACAGTGTGCAGTGGCC
AAATGCTGGAGGGAGCTGAGCTCTGCAGGAACCCGGCACTGGAGAAACCATGTGGGGCTAAGAAACAGAGAAAAG
CTGTTTTTCGGGNNNNNNNATGAATGAAATGGAGAGGCAAGAACTGGAAATAGCAAGACGAGGTATCATGCTACT
GCAATAGTCCAGGCAAAACATGATAAAGGCCCTCAACAAGAATGGCACCAGTGGAGATGAAGAGCAGAAGATCAAG
GTGGGAGACAGAGACAGAGAAAAACAAAGGATTTGATGGCTTATTAGATGTTTGGAATACTTTAAACTTTTATTCAT
CCTTGCTTTGCTGTGTGCAACTGTGTGCATGGGGTGTGCAACAGTGGACTAGATGGCGATGGAAACCTGTGAGTGC
TACTCTGCGTACACTGGCCCCAAGTGTGACAAAGCTCACAGAAAACCTTTCACACCTCTCATCTGACACTGTGGCCT
GTGCACGACTCCAAGCACTGGGGAAGCCTTCGACATCAGAATATGAATGGCACCTGTTCTTCCGGGGGCGGCAAG
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AACAGACGAAGTAGTGTCAAGCGTCTGAGAAGTGAAGGGGGACGATCGAGATGGAGGTGGCAAGGAAGGCCAG
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GTTACCCCTACGGTTTCACTCCTTGACAGAAATGATTCCTTTTCACTCATTCACCAGCAGACTGAAGGAATTT
GAGAAACAGCAGGTGAAGGAAAGATTTTCTGACCCCTCCCTTAATGCAGGCTATAAAACCCCTCACATGAGAAGTAC
CCTCCTTATGCCCAGAGAAAAGGAACATCTTTGTCTCCAAAGACACAGGGACACGGAGATGATGAACAGGCCTTG
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AATATGATGGGCCTGGACAGATGCATTTGCCAGAAAAGGTTACGTGGGTGATGGCTTAACGTGTTATGGAAACATT
ATGGAGCGACTCAGAGAATTAAATACTGAACCCAGAGGAAAATGGCAAGGAAGGCTGACCTCTTTCATCTCACTC
CTAGAAAGTATACAAATTGTAAGTGTACAACCTCAGTGAATTTTCCCAACGTGAACCTACTTGTGTAAACACCAAG
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TTAGATGAGGATGGAGTTGGTGGACCATAACCATTTTGTTCCAAATAATGAAGCATTGAATAACATGAAGGAC
GGCACTCTCGATTACCTCCTTTCTCCAGAGCTTGAAGTGGCCACTCTCATCTCCACCCCTCACATCAGGAGCATG
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GAGATCACTGCCAAAAATGGCCGAATTTACACACTGACAGGAGTTCTCATTCTCCCTCCATTGTCCCATTCTG
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CTAGGCACATACAGAGTGGCAGATCTGCAGACCCTGTCTTCTCTGACATGTTGGCAACATCTTTCAGGGCAAC
TTCCTTCACTTGGCAAAGGTGGATGGGAATATCACAATTGAAGGGGCTCCATTGTGATGGGGACAACGCAGCC
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ATTGAGGCTGCCGATGCCTACACAGTGTCTTGTCTCAAACAACAATGCCATCGAGAATTACATCAGGGAGAAGAAA
GTCTTGTCTCTAGAGGAGGACGTCTCCGGTATCATGTGGTCTGAGGAGAACTCCTGAAGAATGACCTGCAC
AATGGCATGTGAGACCATGCTGGGTTTCTCCTATTCTCTTAGCTTCTTCTCCATAATGACCAGCTCTAT
GTAAATGAGGCTCCAATAAACTACACCAATGTAGCCACTGATAAGGGAGTGATCCATGGTTTGGGAAAAGTTCTG
GAAATTGAGAAGACAGATGTGATAATAATGACACTACTATTATACGAGGAAGATGTAGGACATGCTCCTCAGAG
CTGACCTGCCCATTCGGAATAAATCTCTAGGTAATGAGAAGAGGAGATGCATCTATACCTCTTATTTTCATGGGA
AGACGAACCTGTCTTATTTGGGTGCCAGCCAAATGTGTGAGAAGACCGTCATTACGAGAGAATGCTGTGCCGGCTTC
TTTGGCCCCAATGCCAGCCCTGTCCAGGGAATGCCAGAATGTCTGCTTTGGTAATGGCATCTGTTTGGATGGA
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CCGTGTTTGGAGAACCATGGTGGCTGTGACAAGAATGCGGAGTGCACACAGACAGGACCCAAACAGGCTGCCTGT
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TTGCAGGAGCATTTCGTGAAAGATCTGGTCCGCCAGGCCCCCTTCACTGTTTTTGCACCTTTATCTGCAGCCTTT
GATGAGGAAGCTCGGGTTAAAGACTGGGACAAATACGGTTAATGCCCCAGGTTCTTCCGTACCATGTGGTCCGC
TGCCACCAGCTGCTTCTGAAAACCTGAAATGTATCTCAATGCTACTTCCCTCCAAGGAGAGCCAATAGTCATC
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CCAGATGCCCCGTGTAATAACCGGGTGTCTGCCTTGATCAGTACTCGGCCACCGGAGAGTGTAAATGCAACACC
GGCTTCAATGGGACGGCGTGTGAGATGTGCTGGCCGGGGAGATTTGGGCCTGATTGTCTGCCCTGTGGCTGCTCA
GACCACGGACAGTCCGATGATGGCATCAGGGCTCCGGGAGTGCCTCTGTGAAACGGGTTGGACAGGCCCTCG
TGTGACACTCAGGAGTTTTCCTGCTGAGTGTGTACGCCTCTTGTCTGCTCATGCCACCTGTAAGGAGAACAC
ACGTGTGAGTGTAACTGGATTATGAAGGTGACGGAATCATATGCACAGTTGTGGATTCTGCAAAACAGGACAAC

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GGGGGCTGTGCAAAGGTGGCCAGATGCTCCCAGAAGGGCACGAAGGTCTCCTGCAGCTGCCAGAAGGGATACAAA
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TGTAAGATGACAGGCCCGGGCAAGCACAAAGTGTGAGTGTAAAAGTCACTATGTGCGAGATGGGCTGAACTGTGAG
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CACTTCCAGGATACCACTGTTGGGGTGTTCATCTACGCTCCCCACTGGGCCAGTATAAGCTGACCTTTGACAAA
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CGGATGAAGGAAGTGCTGGCCTATTCCAACAGCTCAGCTCGAGGCCGTGCATTTCTAGAACACCTGACTGACCTG
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CCCGTGACCTTGACCCACACTGGCTTGGGAGCAGGGATCTTCTTTTGCATCATCCTGGTGAATGGGGCTGTTGCC
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GTACTCTTCAGCTGGCACCCTGCTCCATTCTGCCCTACATGATGGGTAACTGTGATCTTTCTTCCCTGTTAGATTG
TAAGCCTCCGTCTTTGTATCCCAGCCCTAGCCAGTGCCCTGACACAGGAACTGTGCACAATAAAGGTTTATGGA
ACAGAAACAAAGTCAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

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The sequence of NOV1a was derived by laboratory cloning of cDNA fragments, by *in silico* prediction of the sequence. The cDNA fragments covering either the full length of the DNA sequence, or part of the sequence, or both, were cloned. *In silico* prediction was based on sequences available in CuraGen's proprietary sequence databases or in the public human sequence databases, and provided either the full length DNA sequence, or some portion thereof.

The DNA sequence and protein sequence for a novel stabilin-like gene were obtained by SeqCallingTM Technology and are reported here as NOV1a. These methods used to amplify NOV1a cDNA are described in Example 2.

The NOV1a polypeptide (SEQ ID NO:2) encoded by SEQ ID NO:1 is 2675 amino acid residues in length and is presented using the one-letter amino acid code in Table 1B. The SignalP, Psort and/or Hydropathy results predict that NOV1a has a signal peptide and is likely to be localized extracellularly in the plasma membrane with a certainty of 0.6760. In alternative embodiments, a NOV1a polypeptide is located to the endoplasmic reticulum (membrane) with a certainty of 0.1000, the endoplasmic reticulum (lumen) with a certainty of 0.1000, or outside the cell with a certainty of 0.1000. The SignalP predicts a likely cleavage site for a NOV1a peptide between amino acid positions 20 and 21, i.e. at the dash in the sequence STG-QC.

Table 1B. Encoded NOV1a Protein Sequence (SEQ ID NO:2)

MGLRSLGLLAVLPLPESSTGQCAVAKCWRELSSAGTRHWRNHVGLRNREKLFFGXMMNEMERQETGNSKTRYHAT
 AIVQAKHDKGLNKNKGTSGDEEQIKVGDRENGKFDGLLDVWNTLNFHPCFAVCNCVHGVCSGLDGDGTCEC
 YSAYTGPKCDKLTENFHTSHLTLWPVHDSKHWGSLRHQNMNGTCSSGGGKGDPDVYQNGLIFHGGGTSGGLSSSR
 NRRSSVKRPEKWKGGDDRDGGGKEGQORRRADTESSLORGHIKTPLPHRQGEARITETTGNVCVSAGMTGTNANHTK
 VHPTVQSLTEYDSFQTHSTSRLEFEKQOVKERFSDPPLMQAIKPSHEKYPPYAQRKGTSLSPKTOGHGDDEQAL
 LSFLHSITLSLYLYPTTFFHDSPVFIKPGIKTLRLNHFSGSSFPYEGSSVIXXMGIEVWKNWCQADTLAAAPAP
 SLNVQPCSAQKIPDVRPLPKMKTNNANAFPI TEAMANTATPSIHVYKSATLMLIVRTWDQIGTVVHAKKATVG
 MAKACALWTPAKLTLETALQSLOCANMMGLDRCICQKGYVGDGLTCYGNIMERLRELNTEPRGKWQGRLTSTFISL
 LESIQIVSVQLSEFSQREPTCVNTKSIASNLEGLVPLSLNHYPLQVNEELLVDNKAQYFVKLHI IAGOMNIEYMN
 NTDMFYTLTGKSGEIFNSDKDNQIKLKLHGGKKIKVQIIGDIIASNGLLHILDRAMDKLEPTFESNNEETNLGHA
 LDEDGVGGPYTIFVPNNEALNNMKDGTLDYLLSPELEVATLISTPHIRSMANQLIQFNTTNDNGQILANDVAMEEI
 EITAKNGRIYTLTGVLIPPSIVPILPHRCDETKREMKLGTVCVSCSLVYWSRCPANSEPTALFTHRCVYSGRFGSL
 KSGCARYCNATVKCADSLGGNGTCICEEGFQGSQCQPCSDPNKYGPRCNKCLCVHGTCCNNRIDS DGACLTGTCTCR
 DGSAGRLCDKQTSACGPYVQFCHIHATCEYSNGTASCICKAGYEGDGLTLCSEMDPCTGLTPGGCSRNAECIKTGT
 GTHTCVCQQGWTGNGRDCSEINCLLPSAGGCHDNASCLYVPGQNECECKKGFRNGIDCEPITS CLEQTGKCH
 PLASCQSTSSGVWSCVCQEGYEGDGLFCYGNAAVELSLSEAAIFNRWINNASLOPTLSATSNTLVLPVPSQOATE
 DMDQDEKSFWLSQSNIPALIKYHMLLGTYRVADLQTLSSSDMLATSLQGNFLHLAKVDGNITIEGASIVDGDNA
 TNGVIHI INKVLVPQRRLTGSLPNLLMRLEQMPDYSIFRGYIIQYNLANATEAADAYTVFAPNNNAIENYIREKK
 VLSLEEDVLRYHVVLEEKLLKNDLHNGMHRETMLGFSYFLSFFLHNDQLYVNEAPINYNVATDKGVIHGLGKVL
 EIQKNRCDNNDTTIIRGRCRTCSSELTCPFGTKSLGNEKRRCIYTSYFMGRRTLFIGCQPKCVRTVITRECCAGF
 FGPQCQPCPGNAQNVCFNGICLDGVNGTGVCEGEGFSGTACETCTEGKYGIHCDQACSCVHGRCNQGPLDGS
 CDCDVGWRGVHCDNATTEDNCNGTCHTSANCLTNSDGTASCKCAAGFQNGTICTAINACEISNGGCSAKADCKR
 TTPGRRVCTCKAGYTGDIIVCLEINPCLENHGGCDKNAECTQTGPNQAACNCLPAYTGDGKVC'TLINVCLTKNGG
 CGEFAICNHTGQVERTCTCKPNYIGDGTFCRGSIIYQELPKNPKTSQYFFQLQEHFVKDLVGPFPFTVFAPLSAAF
 DEEARVKDWDKYGLMPQVLRHYVACHQLLENLKLISNATSLOGEPIVSVSOSTVYINNKAIISSDIISTNG
 IVHIIIDKLLSPKNLLITPKDNSGRILQNLTTLATNNGYIKFSNLIQDSGLLSVITDPIHTPVTLFWPTDQALHAL
 PAEQQDFLFDNKNKDKLKEYLKFHVIRDAKVLAVDLPTSTAWKTLQGSSELSVKCGAGRDIGDLFLNGQTCRIVQR
 ELLFDLGVAYGIDCLLIDPTLGGRCDTFTTFDASGECGSCVNTSPSCPRWSKPKGVKQKCLYNLPFKRNLEGCRER
 CSLVIQIPRCCCKGYFRDQCACPGGPDAPCNNRGVCLDQYSATGECKCNTGFNGTACEMCWPGRFGPDCLPCGCS
 DHGQCDGIGTSGQCLCETGWTGPSCTQAVLPVCTPPCSAHATCKENNTCECNLDYEGDGTCTTVVDFCKQDN
 GGCAKVARCSQKGTKVSCSCQKGYKGDGHSCTEIDPCADGLNGGCHHATCKMTGPGKHKCECKSHYVGDGLNCE
 PEQLPIDRCLQDNGQCHADAKCVDLHFQDTTVGVFHLRSLPLGQYKLTFDKAREACANEAAATMATYNQLSYAQKAK
 YHLCASAGWLETGRVAYPTAFASQNCGSGVVGIVDYGPRPNKSEMWDVFCYRMKEVLAYSNS SARGRAFLHLTDL
 SIRGTLFVFPQNSGLGENETLSGRDIEHHLANVSMFFYNDLVNGTTLQTRLGSKLLITASQDPLQPVQSRFVDGRA
 ILQWDIFASNGIITHVTSRLKAPPAPVTLTHTGLGAGITFCIILVTGAVALAAYSIFRINRRTIGYQHFSEEDI
 NVAALGKQQPENISNPLYESTTSAPPEPSYDPFTDSEERQLEGNDPLRTL

NOV1b

In an alternative embodiment, a NOV1 variant is NOV1b (alternatively referred to herein
 5 as CG50736-10), which includes the 8495 nucleotide sequence (SEQ ID NO:3) shown in Table
 1C. An open reading frame for the mature protein was identified beginning at nucleotides 201-
 203 and ending at nucleotides 7461-7463. The start and stop codons of the open reading frame
 are highlighted in bold type. Putative untranslated regions, found upstream from the initiation
 codon and downstream from the termination codon, are underlined.

Table 1C. NOV1b Nucleotide Sequence (SEQ ID NO:3)

AATCATCCCACATGCTAAGAATCTAAGATGTATAAAATAAAGTGGTGAAAGATGAAAATGAAATTTTATCAAG
 GTTAGAGTCAGGTTGGAGTGGCCATTGTTTACCAAAC TGAGAAATCTAAATTTTATTTGGTTGGTAATTGAGA
 GTCATTGAGATATTTTGGGGAAGGTCACCCCTGATGCCTTTGCTAATCAAATGAAATGAATGAAATGGAGAGGC
 AAGAACTGGAAATAGCAAGACGAGGTATCATGCTACTGCAATAGTCCAGGCAAAACATGATAAAGGCCTCAA
 CAAGAATGGCACCAGTGGAGATGAAGAGCAGAAGATCAAGGTGGGAGACAGAGACAGAGAAAAACAAGGATTT
 GATGGCTTATTAGATGTTTGAATACTTTAAACTTTATTTCATCCTTGCTTTGCTGTGTGCAACTGTGTGCATG
 GGGTGTGCAACAGTGGACTAGATGGCGATGGAACCTGTGAGTGTCTACTCTGCGTACACTGGCCCCAAGTGTGA
 CAAGCTCACAGAAAACCTTTCACACCTCTCATCTGACACTGTGGCCTGTGCACGACTCCAAGCACTGGGGAAGC
 CTTCGACATCAGAATATGAATGGCACCTGTTCTTCCGGGGGCGGCAAGGGGGATCCCAGATGTTTATCAAAATG
 GGTGATTTTCCACGGAGGGGGTACTTCTGGAGGTCTATCGTCATCACGAAACAGACGAAGTAGTGTCAAGCG
 TCCTGAGAAGTGGAAGGGGGACGATCGAGATGGAGGTGGCAAGGAAGGCCAGCAGCGGGCGGGCAGACACA
 GAGTCGAGTCTTCAAAGAGGTACATCAAACGCCCCTGCCCCACAGGCAAGGTGAAGCGCGGATCACGGAGA
 CAACGGGGAATTGTGTTTCTGCTGGCATGACTGGAACCAATGCCAATCACACAAAAGTTACCCCTACGGTTCA
 GTCCTTGACAGAATATGATTCCTTTCAGACTCATTCACCAGCAGACTGAAGGAATTTGAGAAACAGCAGGTG
 AAGGAAAGATTTTCTGACCTCCCTTAATGCAGGCTATAAAACCTCACATGAGAAGTACCCTCCTTATGCC
 AGAGAAAAGGAACATCTTGTCTCCAAAGACACAGGACACGGAGATGATGAACAGGCTTGCTAAGTTTCTCT
 CCACTCTATTACCTTAGCTTGACCTTTATCCAACACATTCCTTCATGACTCTCCAGTCTTCATCAAAACCT
 GGCATAAAAACTCAGACTTAACCACTTCTTTGGGTCTTCATTTCTTATGAAGGCTCCAGTGTCTANNNN
 NNATGGGAATTGAGGTTTGGAAAACTGGTGCCAAATGCTGATACCCTGGCTGCTGCCCCCTGCTCCATCCCT
 GAATGTGCAGCCTTGCTCTGCCAGAAAATTCAGATGTTTCGCTTCCACTGAAGATGAAAACAACTGGAAT
 GCAAATGCCTTCCCAATTACCGAGGCGATGGCAAATACTGCGACCCCATCAATCCATGTTTACGAAAAATCTG
 CCACCTCATGCTCATTGTACGTACCTGGGACCAATCGGCACAGTTGTACATGCCAAGAAGGCTACCGTGGG
 GATGGCCAAGTGTGCTTGCTGTGGACCCCTGCCAAATTAACCTTTGGAACTGCCCTACAAAGTCTACAGTGT
 GCAAATATGATGGGCTGGACAGATGCATTTGCCAGAAAGGTTACGTGGGTGATGGCTTAACGTGTTATGGAA
 ACATTTATGGAGCGACTCAGAGAATTAAATACTGAACCCAGAGGAAAATGGCAAGGAAGGCTGACCTCTTTCAT
 CTCACTCCTAGAAAGTATACAAATTTGTAAGTGTACAACCTCAGTGAATTTTCCCAACGTGAACCTACTTGTGTA
 AACACCAAGTCCATTGCCAGCAACCTAGAAGGCCCTTGGTCCCCCTTCCCAATCATTACCCTCTACAGGTAA
 ATGAGCTTTTGGTGGATAATAAAGCTGCTCAATACTTTGTGAACTCCACATAATTGCTGGTCAGATGAACAT
 CGAATATATGAATAACACAGACATGTTCTACACCTTGACTGGAAAGTCGGGGGAATCTTCAACAGCGATAAG
 GACAATCAAATAAAGCTTAAACTCCATGGAGGCAAAAAGAAGGTAAAAATTATACAAGGGGACATCATTGCTT
 CCAATGGGCTTCTGCACATCCTTGACAGAGCCATGGACAAATTAGAACCCACATTTGAGAGCAAAATGAGGA
 AACCAATTTGGGACATGCCTTAGATGAGGATGGATTTGGTGGACCACATACACCATTTTGTTCCAAATAATGAA
 GCATTGAATAACATGAAGGACGGCACTCTCGATTACCTCTCTTCTCCAGAGCTTGAAGTGGCCACTCTCATCT
 CCACCCCTCACATCAGGAGCATGGCCAACCCAGCTCATAAGTTCAACACCACCGACAATGGACAGATTCTGGC
 AAATGATGTGGCAATGGAAGAAATTGAGATCACTGCCAAAAATGGCCGAATTTACACACTGACAGGAGTTCTC
 ATTCTCCCTCCATTGTCCCGATTCTGCCCATCGATGTGATGAAACAAAGAGAGAGATGAAACTGGGCACTT
 GTGTGAGCTGTTCTCTGGTGTACTGGAGCAGATGTCTGCTAATCTGAGCCACAGCACTCTTACACACAG
 ATGTGTCTACAGTGGCAGGTTTGGGAGCCTGAAGAGCGGCTGTGCCCGGTACTGCAATGCCACTGTGAAGTGT
 GCAGATAGCCTCGGCGGCAACGGGACATGCATTTGTGAGGAGGGCTTCCAAGGCTCCAGTGTGAGTTCTGCT
 CTGATCCCAATAAATACGGACCTCGGTGTAACAAAAATGCCTGTGCGTTACGGAACATGCAATAACAGGAT
 AGACAGCGATGGGGCCTGCCTCACTGGCACATGCAGAGACGGCTCTGCCGGGAGACTCTGTGATAAGCAGACC
 TCAGCCTGTGGGCCCTACGTGCAGTTCTGTACATCCACGCCACCTGTGAATACAGCAATGGGACAGCCAGTT
 GTATTTGCAAAGCAGGATATGAAGGAGATGGAACCTCTGTGTTCTGAGATGGACCTTGCACAGGACTAATCC
 AGGAGGCTGTAGCCGCAATGCAGAATGCATCAAACTGGCACGGGCACCCACACCTGCGTGTGTGACAGGGT
 TGGACAGGGAATGGGAGAGACTGCTCGGAGATCAACAACTGCCGTGCTGCCAGTGCAGGCGGCTGCCACGACA
 ACGCATCCTGTTGTATGTGGGTCCCGGGCAGAATGAGTGTGAGTGCAAGAAAGGATTTGAGGAAATGGGAT
 TGAATGTGAACCAATAACTTCATGCTTGGAAACAAACCGGGAATGTATCCATTGGCAAGCTGTCAATCTACT
 TCGTCTGGTGTCTGGAGCTGTGTTGTCAAGAGGGCTATGAAGGAGATGGCTTTCTGTGCTATGGAACGCAG
 CAGTGAATTTGTCATTTCTCTCCGAAGCAGCTATATTTAACCAGTGGATAAATAATGCTTCTCTACAACCCAC
 ACTGTCAGCCACCTCAAACCTCACTGTCTCTGCTTCCCAACAAGCTACTGAGGACATGGACCAGGATGAG
 AAAAGCTTCTGGTTGTACAGAGCAATATTCAGCCCTAATAAAGTACCATATGCTACTAGGCACATACAGAG
 TGGCAGATCTGCAGACCCTGTCTTCTCTGACATGTTGGCAACATCTTTCAGGGCAACTTCTTCACTTGGC

AAAGGTGGATGGGAATATCACAATTGAAGGGGCTCCATTGTGCGATGGGGACAACGCAGCCACAAATGGAGTG
ATACACATCATCAACAAGGTGCTGGTCCCACAAAGACGTCTAACTGGCTCCTTACCAAACCTGCTCATGCGGC
TGGAACAGATGCCTGACTATTCCATCTTCCGGGGCTACATCATTCAATATAATCTGGCGAATGCAATTGAGGC
TGCCGATGCCTACACAGTGTGCTCCAAACAACAATGCCATCGAGAATTACATCAGGGAGAAGAAAGTCTTG
TCTCTAGAGGAGGACGTCTCCGGTATCATGTGGTCTGAGGAGAACTCCTGAAGAATGACCTGCACAATG
GCATGCATCGTGAGACCATGCTGGGTTTCTCCTATTTCTTAGCTTCTTTCTCCATAATGACCAGCTCTATGT
AAATGAGGCTCCAATAAACTACACCAATGTAGCCACTGATAAGGGAGTGATCCATGGTTTGGGAAAAGTTCTG
GAAATTCAGAAGAACAGATGTGATAATAATGACACTACTATTATACGAGGAAGATGTAGGACATGCTCCTCAG
AGCTGACCTGCCCAITTCGGAACATAATCTCTAGGTAATGAGAAGAGGAGATGCATCTATACCTCCTATTTTCAT
GGGAAGACGAACCCCTGTTTTATTGGGTGCCAGCCAAAATGTGTGAGAACCCTCATTACGAGAGAATGCTGTGCC
GGCTTCTTTGGCCCCCAATGCCAGCCCTGCCAGGGAATGCCAGAATGTCTGCTTTGGTAATGGCATCTGTT
TGGATGGAGTGAATGGCACAGGTGTGTGTGAGTGTGGGAGGGCTTCAGCGGCACAGCCTGCGAGACCTGCAC
CGAGGGCAAGTACGGCATCCACTGTGACCAAGCATGTTCTGTGTCCATGGGAGATGCAACCAAGGACCCCTG
GGAGATGGCTCCTGTGACTGTGATGTTGGCTGGCGAGGAGTGCAATTGTGACAATGCAACCAAGGACCACT
GCAATGGGACATGCCATACCAGCGCCAACTGCCTCACCACCTCAGATGGTACAGCTTCATGCAAGTGTGCAGC
AGGATTCGAAGGAAACGGGACCATCTGCACAGCAATCAATGCCTGTGAGATCAGCAATGGAGTTGCTCTGCC
AAGGCTGACTGTAAGAGAACCACCCAGGAAGGCGAGTGTGCACGTGCAAAGCAGGCTACACGGGTGATGGCA
TTGTGTGCCTGGAAATCAACCCGTGTTTGGAGAACCATGGTGGCTGTGACAAGAATGCGGAGTGACACAGAC
AGGACCCAACAGGCTGCCTGTAACCTGTTTGCAGCATACACTGGAGATGGAAAGGTCTGCACACTCATCAAT
GTCTGTCTAACTAAAAATGGCGGCTGTAGTGAATTTGCCATCTGCAACCACACTGGGCAAGTAGAAAGGACTT
GTACTTGCAAGCCAACTACATTGGAGATGGATTTACCTGCCGCGGCAGCATTTATCAGGAGCTTCCCAAGAA
CCCGAAAACCTCCAGTATTTCTTCCAGTTGCAGGAGCATTTCTGTGAAAGATCTGGTGGGCCAGGCCCTTC
ACTGTTTTTGCACCTTTATCTGCAGCCTTTGATGAGGAAGCTCGGGTTAAAGACTGGGACAAATACGGTTTAA
TGCCCCAGGTTCTTCGGTACCATGTGGTGCCTGCCACCAGCTGCTTCTGGAAAACCTGAAATTGATCTCAAA
TGCTACTTCCCTCCAAGGAGAGCCAATAGTCATCTCCGTCTCTCAGAGCACGGTGTATATAAACAATAAGGCT
AAGATCATATCCAGTGATATCATCAGTACTAATGGGATTGTTCATATCATAGACAAATTGCTATCTCCCAAAA
ATTTGCTTATCACTCCCAAAGACAACCTCTGGAAGAATTCTGCAAAATCTTACGACTTTGGCAACAACAATGG
CTACATCAAATTTAGCAACTTAATACAGGACTCAGGTTTGTCTGAGTGTCTATCACCAGTCCCATCCACACCCCA
GTCACCTCTCTTCTGGCCCCACCGACCAAGCCCTCCATGCCCTACCTGCTGAACAACAGGACTTCC
TGTTCAACCAAGACAACAAGGACAAGCTGAAGGAGTATTTGAAGTTTCATGTGATACGAGATGCCAAGGTTTT
AGCTGTGGATCTTCCACATCCACTGCCTGGAAGACCCTGCAAGGTTTCAAGAGTGTGATGAGATGCCAAGGTTTT
GGCAGGGACATCGGTGACCTCTTCTGAATGGCCAAACCTACAGAATTGTGCAGCGGGAGCTCTTGTGTTGACC
TGGGTGTGGCCTACGGCATTGACTGTCTGCTGATTGATCCACCCCTGGGGGGCCGCTGTGACACCTTTACTAC
TTTCGATGCCTCGGGGGAGTGTGGGAGCTGTGTCAATACTCCAGCTGCCCAAGGTGGAGTAAACCAAAGGTT
GTGAAGCAGAAGTGTCTCTACAACCTGCCCTTCAAGAGGAACCTGGAAGGCTGCCGGGAGCGGTGCAGCCTGG
TGATACAGATCCCCAGGTGCTGCAAGGGCTACTTCGGGCGAGACTGTGAGGCTGCCCTGGAGGACCAGATGC
CCCGTGTAAATAACCGGGGTGTCTGCCTTGATCAGTACTCGGCCACCGGAGAGTGTAAATGCAACACCGGCTTC
AATGGGACGGCGTGTGAGATGTGCTGGCCGGGGAGATTGCGGCTGATTGTCTGCCCTGTGGCTGCTCAGACC
ACGGACAGTGCAGATGATGATGATGCTGGCCGGGGAGATTGCGGCTGATTGTCTGCCCTGTGGCTGCTCAGACC
TGACACTCAGGCAGTTTTCCTGCTGAGTGTGTACGCTCCTTGTCTGCTCATGCCACCTGTAAGGAGAACAAC
ACGTGTGAGTGTAACTGGATTATGAAGGTGACGGAATCACATGCACAGTTGTGGATTTCTGCAACAGGACA
ACGGGGGCTGTGCAAGGTGGCCAGATGCTCCCAAGGGACGGAAGGTCTCCTGCAGCTGCCAGAAGGGATA
CAAAGGGGACGGGCACAGCTGCACAGAGATAGACCCCTGTGACAGACGGCCTTAACGGAGGGTGTACAGGAC
GCCACCTGTAAGATGACAGGCCCGGGCAAGCACAAGTGTGAGTGTAAAGTCACTATGTGCGAGATGGGCTGA
ACTGTGAGCCGGAGCAGCTGCCCATTTGACCGCTGCTTACAGGACAATGGGCAGTGCATGCAGACGCCAAATG
TGTGACCTCCACTTCCAGGATAACACTGTTGGGGTGTTCATCTACGCTCCCCACTGGGCGAGTATAAGCTG
ACCTTTTGACAAAGCCAGAGAGGCTGTGCCAAGCAAGCTGCGACCATGGCAACCTACAACAGCTCTCCTATG
CCCAGAAGGCCAAGTACCACCTGTGCTCAGCAGGCTGGCTGGAGACCGGGCGGGTTCCTACCCACAGCCTT
CGCCTCCCAGAACTGTGGCTCTGGTGTGGTTGGGATAGTGGACTATGGACCTAGACCCAACAAGAGTGAAATG
TGGGATGTCTTCTGCTATCGGATGAAAGGAAGTGTGGCCTATTCCAACAGCTCAGCTCGAGGCCGTGCATTT
CTAGAACACCTGACTGACCTGTCCATCCGCGGCACCCCTCTTTGTGCCACAGAACAGTGGGCTGGGGGAGAATG
AGACCTTGTCTGGGCGGGACATCGAGCACCACCTCGCCAATGTGAGCATGTTTTTCTACAATGACCTTGTCAA
TGGCACCACCCCTGCAACGAGGCTGGGAAGCAAGCTGCTCATCTGCCAGCCAGGACCCACTCCAACCGACG
GAGACCAGGTTTGTGATGGAAGAGCCATTCTGCAGTGGGACATCTTTGCCTCCAATGGGATCATTCATGTCA
TTTCCAGGCCTTTAAAGACACCCCTGCCCGGCTGACCTTGACCCACACTGGCTTGGGAGCAGGGATCTTCTT
TGCCATCATCTGGTGAAGTGGGCTGTTGCCCTGGCTGCTTACTCCTACTTTCCGATAAACCAGGAGAACAATC
GGCTTCCAGCATTTTGAAGTCCGAAGAGGACATTAATGTTGCAGCTCTTGGCAAGCAGCAGCTGAGAATATCT


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CGAACCCCTTGTATGAGAGCACAACTCAGCTCCCCAGAACCTTCCTACGACCCCTTCACGGACTCTGAAGA
ACGGCAGCTTGAGGGCAATGACCCCTTGAGGACACTGTGAGGGCCTGGACGGGAGATGCCAGCCATCACTCAC
TGCCACCTGGGCCATCAACTGTGAATTCTCAGCACCAGTTGCCTTTTAGGAACGTAAAGTCCTTTAAGCACTC
AGAAGCCATACCTCATCTCTCTGGCTGATCTGGGGTTGTTTCTGTGGGTGAGAGATGTGTTGCTGTGCCAC
CCAGTACAGCTTCTCTCTGACCCTTTGGCTCTTCTCCTTTGTACTCTTCAGCTGGCACCTGCTCCATTCT
GCCCTACATGATGGGTAACTGTGATCTTTCTTCCCTGTTAGATTGTAAGCCTCCGTCTTTGTATCCCAGCCCC
TAGCCCACTGCCTGACACAGGAAGTGTGCACAATAAAGGTTTATGGAACAGAAACAAAGTCAAAAAAAAAA
AAAAAAAAAAAAAAAAAAAAAAAAAAC

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The sequence of NOV1b was derived by laboratory cloning of cDNA fragments, by *in silico* prediction of the sequence. The cDNA fragments covering either the full length of the DNA sequence, or part of the sequence, or both, were cloned. *In silico* prediction was based on sequences available in CuraGen's proprietary sequence databases or in the public human sequence databases, and provided either the full length DNA sequence, or some portion thereof.

The DNA sequence and protein sequence for a novel stabilin-like gene were obtained by SeqCalling™ Technology and are reported here as NOV1b. These methods used to amplify NOV1b cDNA are described in Example 2.

The NOV1b polypeptide (SEQ ID NO:4) encoded by SEQ ID NO:3 is 2420 amino acid residues in length and is presented using the one-letter amino acid code in Table 1D. The SignalP, Psort and/or Hydropathy results predict that NOV1b has no known signal peptide and is likely to be localized in the cytoplasm with a certainty of 0.4500. In alternative embodiments, a NOV1b polypeptide is located to the microbody (peroxisome) with a certainty of 0.3000, the mitochondrial matrix space with a certainty of 0.1000, or the lysosome (lumen) with a certainty of 0.1000.

Table 1D. Encoded NOV1b Protein Sequence (SEQ ID NO:4)

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MNEMERQETGNSKTRYHATAIVQAKHDKGLNKNGTSGDEEQKIKVGDRDRENKGF DGLLDVWNTLNF IHP CFAV
CNCVHGVCNSGLDGDGTCECYSAITGPKCDKL TENFHTSHLTLWPVHDSKHWSLRHQNMNGTCS SGGGKGDPD
VYQNGLI FHGGGTSGGLSSSRNRSSVKRPEKWKGD DRDGGGKEGQRRRADTESSLQRGHIKTPLPHRQGEAR
ITETTGNCVSAGMTGTNANHTKVHPTVQSLTEYDSFQTHSTSR LKEFEKQVKERFSDPPLMQA IKPSHEKYPP
YAQRKGTSLSPKTQGHGDDEQALLSFLHSITLSLYLYPTTFFHDS PVFIKPGIKTLRLNHFFGSSFPYEGSSVI
XXMGIEVWKNWCQNADTLAAAPAPSLNVQPCSAQKIPD VRLPLKMKTNWNANAFPITEAMANTATPSIHVYEKS
ATLMLIVRTWDQIGTVVHAKKATVGMACACLWTPAKLTLETALQSLQCANMMGLDR C ICKGYVGDGLTCYGN
IMERLRELNTEPRGKWQGR L TSFISLLESIQIVSVQLSEFSQREPTCVNTKSIASNLEGPLVPLSNHYPLQVNE
LLVDNKA AQYFVKLHI IAGQMNIEYMNNTDMFYTLTGKSGE I FNSDKDNQIKLKLHGGKKVKI IQGDI IASNG
LLHILDRAMDKLEPTFESNNEETNLGHALDEDGVGGPYTIFVPNNEALNNMKDGTLDYLLSPELEVATLISTPH
IRSMANQLIQFNTTDNGQILANDVAMEEIEITAKNGRIYTLTGVLIPPSIVPILPHRCDETKREM KLGTCVSCS
LVYWSRCPANSEPTALFTHRCVYSGRFGLSKSGCARYCNATVKCADSLGGNGTCICEEGFQGSQCQFCSDPNKY
GPRCNKKCLCVHGTCNNRIDSDGACLTGTCDGSAGRLCDKQTSACGPYVQFCHIHATCEYSNGTASCICKAGY

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EGDGTLCSEMDPCTGLTPGGCSRNAECIKTGTGHTCVCQQGWTGNRDCSEINNCLLPASAGGCHDNASCLYVG
 PGQNECECKKGFGRNGIDCEPITSCLEQTGKCHPLASCQSTSSGVWSCVCQEGYEGDGLCYGNAAVELSFLSE
 AAFNRWINNASLQPTLSATSNTLVLPSSQATEDMDQDEKSFWLSQSNIPALIKYHMLLGTyrVADLQTLSSS
 DMLATSLQGNFLHLAKVDGNITIEGASIVDGDNAATNGVIHI INKVLVPQRRLTGSLPNLLMRLEQMPDYSIFR
 GYIIQYNLANAIEAADAYTVFAPNNNAIENYIREKKVLSLEEDVLRVHVLEEKLLKNDLHNGMHRETMLGFSY
 FLSFFLHNDQLYVNEAPINYTNVATDKGVHGLGVLEIQKNRCDNNDTTIIRGRCRTCSSELTCPFGTKSLGN
 EKRRCIYTSYFMGRRTLFIGCQPKCVRTVITRECCAGFFGPQCQPCPGNAQNVCFGNGICLDGVNGTGVCECGE
 GFSGTACETCTEGKYGIHCDQACSCVHGRCNQGPLGDSCDCDVGWRGVHCDNATTEdNCNGTCHTSANCLTNS
 DGTASCKCAAGFQNGNTICTAINACEISNGGCSAKADCKRTTPGRRVCTCKAGYTDGDIVCLEINPCLENHGGC
 DKNAECTQTGPNQAACNCLPAYTGDGKVCCTLINVLTKNGGCSEFAICNHTGQVERTCTCKPNYIGDGFTCRGS
 IYQELPKNPKTSQYFFQLQEHFVKDLVGPFPFTVFAPLSAAFDEEARVKDWDKYGLMPQVLRVHVACHQLLLE
 NLKLISNATSLQGEPIVISVSQSTVYINNKAIISSDIISTNGIVHIIDKLLSPKNLLITPKDNSGRILQNLTT
 LATNNGYIKFSNLIQDSGLLSVITDPIHTPVTLEFWPTDQALHALHALPAEQQDFLNFQDNKDKLKEYLKFHVIR
 DAKVLAVDLPTSTAWKTLQSELSVKCGAGRDIGDLFLNGQTYRIVQRELLFDLVAYGIDCLLIDPTLGGRC
 TFTTFDASGECGSCVNTFPCPRWSKPKGVKQCLYNLPFKRNLEGCRERCSLVIQIPRCCCKGYFGRDCQACPGG
 PDAPCNMRGVCLDQYSATGECKCNTGFNGTACEMCWPGFRGPDCLPCGCSHDGQCDGIGTSGSQCLCETGWTGP
 SCDTQAVLPAVCTPPCSAHATCKENNTCECNLDYEGDITCTVVDCKQDNNGGCAKVARCSQKGTVCSCQKG
 YKGDGHSCTEIDPCADGLNGGCHAHATCKMTGPGKHCKECKSHYVGDGLNCEPEQLPIDRCLQDNGQCHADAKC
 VDLHFQDTTVGVFHLRSLPGQYKLTDFDKAREACANEATMATYNQLSYAQKAKYHLCSAGWLETGRVAYPTAFA
 SQNCGSGVVGIVDYGPRPNKSEMWDVFCYRMKGSAGLFQQLSSRPCISRTPD

NOV1c

A NOV1 variant includes NOV1c (alternatively referred to as CG 50736-09), which includes the 3260 nucleotide sequence (SEQ ID NO:210) shown in Table 1E.

5

Table 1E. NOV1c Nucleotide Sequence (SEQ ID NO:210)

GGCACGAGCAGGAGCTTCCCAAGAACCCGAAAACCTCCAGTATTTCTTCCAGTTGCAGGAGCATTTCGTGAA
 AGATCTGGTGGGCCAGGCCCTTCACTGTTTTTGCACCTTTATCTGCAGCCTTTGATGAGGAAGCTCGGGTT
 AAAGACTGGGACAAATACGGTTTAATGCCCCAGGTTCTTCCGTACCATGTGGTGCCTGCCACGACTGCTTC
 TGGAAAACCTGAAATTGATCTCAAATGCTACTTCCCTCCAAGGAGAGCCAATAGTCATCTCCGTCTCTCAGAG
 CACGGTGTATATAAATAAAGGCTAAGATCATATCCAGTGATATCATCAGTACTAATGGGATTGTTTCATATC
 ATAGACAAATTGCTATCTCCAAAATTTGCTTATCACTCCCAAAGACAACCTCTGGAAGAATTCTGCAAAATC
 TTACGACTTTGGCAACAACAATGGCTACATCAAATTTAGCAACTTAATACAGGACTCAGGTTTGCTGAGTGT
 CATCACCGATCCCATCCACACCCAGTCACTCTCTTCTGGCCACCGACCAAGCCCTCCATGCCCTACCTGCT
 GAACAACAGGACTTCTGTTCACCAAGACAACAAGGACAAGCTGAAGGAGTATTTGAAGTTTCATGTGATAC
 GAGATGCCAAGGTTTTAGCTGTGGATCTTCCACATCCACTGCCTGGAAGACCCTGCAAGGTTTCAGAGCTGAG
 TGTGAAATGTGGAGCTGGCAGGGACATCGGTGACCTCTTCTGAATGGCCAAACCTGCAGAATTGTGCAGCGG
 GAGCTCTTGTGTTGACCTGGGTGTGGCCTACGGCATTGACTGTCTGCTGATTGATCCACCCCTGGGGGGCCGCT
 GTGACACCTTTTACTATTTTCGATGCCCTCGGGGGAGTGTGGGAGCTGTGTCAATACTCCAGCTGCCCAAGGTG
 GAGTAAACCAAAGGGTGTGAAGCAGAAGTGTCTCTACAACCTGCCCTTCAAGAGGAACCTGGAAGGCTGCCGG
 GAGCGGTGCAGCCTGGTGATACAGATCCCCAGGTGCTGCAAGGGCTACTTCCGGCGAGACTGTCAGGCCTGCC
 CTGGAGGACCAGATGCCCCGTGTAATAACCGGGTGTCTGCCTTGATCAGTACTCGGCCACCGGAGAGTGTAA
 ATGCAACACCGGCTTCAATGGGACGGCGTGTGAGATGTGCTGGCCGGGGAGATTCCGGGCCTGATTGTCTGCCC
 TGTGGCTGCTCAGACCACGGACAGTGCGATGATGGCATCAGGGCTCCGGGCAGTGCTCTGTGAAACGGGGT
 GGACAGGCCCTCGTGTGACACTCAGGCAGTTTTCCTGCAAGTGTGTACGCCTCCTTGTCTGCTCATGCCAC
 CTGTAAGGAGAACAACACGTGTGAGTGTAACTGGATTATGAAGGTGACGGAATCACATGCACAGTTGTGGAT
 TTCTGCAACAGGACAACGGGGGCTGTGCAAGGTGGCCAGATGCTCCAGAAAGGGCACGAAGGTCTCTGCA
 GCTGCCAGAAGGGATACAAAGGGGACGGGCACAGCTGCACAGAGATAGACCCCTGTGCAGAGCCCTTAACGG
 AGGGTGTACAGGACAGCCACCTGTAAGATGACAGGCCCGGCAAGCACAGTGTGAGTGTAAAGTCACTAT
 GTCGGAGATGGGCTGAACTGTGAGCCGGAGCAGCTGCCATTGACCGCTGCTTACAGGACAATGGGCAGTGCC


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ATGCAGACGCCAAATGTGTGACCTCCACTTCCAGGATACCACTGTTGGGGTGTTCCATCTACGCTCCCCACT
GGGCCAGTATAAGCTGACCTTTGACAAAGCCAGAGAGGCCTGTGCCAACGAAGCTGCGACCATGGCAACCTAC
AACCAGCTCTCCTATGCCCAGAAGGCCAAGTACCACCTGTGCTCAGCAGGCTGGCTGGAGACCGGGCGGGTTG
CCTACCCACAGCCTTCGCCTCCCAGAACTGTGGCTCTGGTGTGGTTGGGATAGTGGACTATGGACCTAGACC
CAACAAGAGTGAATGTGGGATGTCTTCTGCTATCGGATGAAAGATGTGAACTGCACCTGCAAGGTGGGCTAT
GTGGGAGATGGCTTCTCATGCAGTGGGAACCTGCTGCAGGTCTGATGTCTTCCCCTCACTCACAACTTCC
TGACGGAAGTGCTGGCCTATTCCAACAGCTCAGCTCGAGGCCGTGCATTTCTAGAACACCTGACTGACCTGTC
CATCCGCGGCACCCTCTTTGTGCCACAGAACAGTGGGCTGGGGGAGAATGAGACCTTGTCTGGGCGGGACATC
GAGCACCACTCGCCAATGTGAGCATGTTTTCTACAATGACCTTGTCAATGGCACCACCCTGCAACGAGGG
TGGGAAGCAAGCTGCTCATCACTGCCAGCCAGGACCCACTCCAACCGACGGAGACCAGGTTTGTGATGGAAG
AGCCATTCTGCAGTGGGACATCTTTGCCTCCAATGGGATCATTGATGTCATTTCCAGGCCTTTAAAGCAGCCC
CCTGCCCCCGTGACCTTGACCCACACTGGCTTGGGAGCAGGGATCTTCTTTGCCATCATCTGCTGACTGGGG
CTGTTGCCTTGGCTGCTTACTCCTACTTTTCGGATAAACCGGAGAACAAATCGGCTTCCAGCATTTTGTGTCGGA
AGAGGACATTAATGTTGCAGCTCTTGGCAAGCAGCAGCCTGAGAATATCTCGAACCCCTTGTATGAGAGCACA
ACCTCAGCTCCCCCAGAACCTTCTACGACCCCTTTCACGGACTCTGAAGAACGGCAGCTTGAGGGCAATGACC
CCTTGAGGACACTGTGAGGGCCTGGACGGGAGATGCCAGCCATCACTCACTGCCACCTGGGCCATCAACTGTG
AATTCTCAGCACCAGTTGCCTTTTAGGAACGTAAAGTCCTTTAAGCACTCAGAAGCCATACCTCATCTCTCTG
GCTGATCTGGGGGTTGTTTCTGTGGGTGAGAGATGTGTTGCTGTGCCACCCAGTACAGCTTCTCTCTGAC
CCTTTGGCTCTTCTCCTTTGTACTCTTCAGCTGGCACCTGCTCCATTCTGCCCTACATGATGGGTAAGTGTG
ATCTTTCTTCCCTGTTAGATTGTAAGCCTCCTTCTTTGTATCCCAGCCCCCTAGCCCAGTGCCTGACACAGGAA
CTGTGCACAATAAAGGTTTATGGAACAGAAAAA

```

The NOV1c polypeptide (SEQ ID NO:211) encoded by SEQ ID NO:210 is 897 amino acid residues in length and is presented using the one letter amino acid code in Table 1F.

Table 1F. Encoded NOV1c Protein Sequence (SEQ ID NO:211)

```

MPQVLRVHVACHQLLENLKLISNATSLQGEPIVISVSQSTVYINNKAIISSDIISTNGIVHIIKLLSPKN
LLITPKDNNGRILQNLTTLATNNGYIKFSNLIQDSGLLSVITDPIHTPVTLEFWPTDQALHALPAEQQDFLFNQD
NKDKLKEYLKFHVIRDAKVLAVDLPTSTAWKTLQGSSELSVKCGAGRDIGDLFLNGQTCRIVQRELLFDLGVAYG
IDCLLIDPTLGGRCDTFTTTFDASGECGSCVNTPSCPRWSKPKGVKQKCLYNLPFKRNLEGCRERCRLVIQIPRC
CKGYFGRDCQACPGGPDPAPCNRGVCLDQYSATGECKCNTGFNGTACEMCWPGRFGPDCLPCGSDHGQCDDGI
TGSGQCLCETGWTGPSCTDQAVLPAVCTPPCSAHATCKENNTCECNLDYEGDGITCTVVDPFCKQDNGGCAKVAR
CSQKGTKVSCSCQKGYKGDGHSCTEIDPCADGLNGGCHEHATCKMTGPGKHKCECKSHYVGDGLNCEPEQLPID
RCLQDNGQCHADAKCVDLHFQDTTVGVFHLRSLPLGQYKLTFDKAREACANEAAATMATYNQLSYAQKAKYHLCSA
GWLETGRVAYPTAFASQNCGSGVVGIVDYGPRPNKSEMWDVFCYRMKDVNCTCKVGYVGDGFS CSGNLLQVLMS
FPSLTNFLTVEVLAYSNS SARGRAFLEHLTDL SIRGTLFVPQNSGLGENETLSGRDIEHHLANVSMFFYNDLVNG
TTLQTRVGSKLLITASQDPLQPTETRFVDGRAILQWDIFASNGIIHVISRPLKAPPAPVTLTHTGLGAGIFFAI
ILVTGAVALAAYSIFRINRRTIGFQHFSEEDINVAALGKQQPENISNPLYESTTSAPPEPSYDPFTDSEERQL
EGNDPLRTL

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5

Searches of the sequence databases revealed that NOV1c has 99% homolgy to a CD44-like precursor FELL-like protein. Included in the invention are variants of the parent clone NOV1c as shown below in Table 1G. These novel variants were derived by laboratory cloning of cDNA fragments coding for a domain of the full length form of NOV1c (CG50736-09), between residues 85 and 636 (Fascilin domain). The cDNA coding for the variant sequences was cloned

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by the polymerase chain reaction (PCR). Primers were designed based on *in silico* predictions of the full length or some portion (one or more exons) of the cDNA/protein sequence of the invention, or by translated homology of the predicted exons to closely related human sequences or to sequences from other species. These primers and methods used to amplify the variant cDNA are described in Example 2.

Table 1G. Variants of NOV1c			
Nov1c Variant No.	Alternate Reference	Change in SEQ ID NO:210	Change in SEQ ID NO:211
1	169487446	T → C at bp 887; and A → T at bp 1144;	Q → L at aa 325
2	169487460	C → T at bp 1034; and T → C at bp 1244;	No change
3	169487473	C → T at bp 1223; A → T at bp 1416; and T → C at bp 1629	N → Y at aa 416; and C → R at aa 487
4	169487491	G → A at bp 1534; and A → G at bp 1547;	S → N at aa 455
5	169487497	A → G at bp 976; and G → A at bp 2010;	K → R at aa 269; and G → S at aa 614
6	169487533	A → G at bp 832; C → T at bp 1223; and T → C at bp 2003	Y → C at aa 221
7	169487538	A → G at bp 513; and T → C at bp 1888;	I → V at aa 115; and M → T at aa 573
8	169487577	G → T at bp 712	No change

SNP variants of NOV1 are disclosed in Example 3.

NOV1 Clones

Unless specifically addressed as NOV1a, NOV1b, NOV1c, or variants of NOV1c, any reference to NOV1 is assumed to encompass all variants.

The amino acid sequence of NOV1 has high homology to other proteins as shown in Table 1H.

Table 1H. BLASTX Results from Patp Database for NOV1

Sequences Producing High-Scoring Segment Pairs:	High Score	Smallest Sum Prob P (N)
patp:AA93910 A human hyaluronan-binding protein, designated WF-HABP	2493	1.2e-290
patp:AA93913 A human hyaluronan-binding protein, designated BM-HABP	848	1.9e-157
patp:AAB42164 Human ORFX ORF1928 polypeptide sequence	1017	1.9e-138
patp:AA93911 A human hyaluronan-binding protein, designated WF-HABP	536	6.1e-75
patp:AAR05222 Antigen GX5401FL encoded by Eimeria tenella genomic DNA	353	4.3e-54

5 In a search of sequence databases, it was found, for example, that the NOV1a nucleic acid sequence has 1593 of 2797 bases (56%) identical to a gb:GENBANK-ID:HSA275213|acc:AJ275213.1 mRNA from Homo sapiens (Homo sapiens mRNA for stabilin-1 (stab1 gene)). Further, the full amino acid sequence of the disclosed NOV1a protein of the invention has 543 of 1391 amino acid residues (39%) identical to, and 760 of 1391 amino acid
10 residues (54%) similar to, the 2570 amino acid residue ptrn:SPTREMBL-ACC:Q9NY15 protein from Homo sapiens (Human) (STABILIN-1).

In a similar search of sequence databases, it was found, for example, that the NOV1b nucleic acid sequence has 2654 of 2678 bases (99%) identical to a gb:GENBANK-ID:HSM801377|acc:AL133021.1 mRNA from Homo sapiens (Homo sapiens mRNA; cDNA
15 DKFZp434E0321 (from clone DKFZp434E0321)). Further, the full amino acid sequence of the disclosed NOV1b protein of the invention has 638 of 642 amino acid residues (99%) identical to, and 638 of 642 amino acid residues (99%) similar to, the 897 amino acid residue ptrn:SPTREMBL-ACC:Q9NRY3 protein from Homo sapiens (Human) (CD44-LIKE PRECURSOR FELL).

20 Additional BLASTP results are shown in Table 1I.

Table 1I. NOV1 BLASTP Results

Gene Index/ Identifier	Protein/Organism	Length of aa	Identity (%)	Positives (%)	Expect Value
Q9UF98	HYPOTHETICAL 115.7 KDA PROTEIN - Homo	1069	1038/1064 (97%)	1042/1064 (97%)	0.0

	sapiens (Human)				
Q9H7H7	FLJ00112 PROTEIN - Homo sapiens (Human)	1192	926/929 (99%)	928/929 (99%)	0.0
Q9NRY3	CD44-LIKE PRECURSOR FELL - Homo sapiens (Human)	897	640/641 (99%)	641/641 (100%)	0.0
Q9NY15	STABILIN-1 - Homo sapiens (Human)	2570	543/1391 (39%)	760/1391 (54%)	0.0
Q93072	MYELOBLAST KIAA0246 PROTEIN - Homo sapiens (Human)	2212	614/1740 (35%)	897/1740 (51%)	0.0

A multiple sequence alignment is given in Table 1J, with the NOV1a and NOV1b proteins of the invention being shown in lines 1 and 2, in a ClustalW analysis comparing NOV1 with related protein sequences of Table 1I.

Table 1J. ClustalW Analysis of NOV1

	1. SEQ ID NO.: 2	NOV1a	5. SEQ ID NO.: 41	Q9NRY3
	2. SEQ ID NO.: 4	NOV1b	6. SEQ ID NO.: 42	Q9NY15
	3. SEQ ID NO.: 39	Q9UF98	7. SEQ ID NO.: 43	Q93072
	4. SEQ ID NO.: 40	Q9H7H7		
15	NOV1a	MGLRSLGLLAVLPLPESSTGQCAVAKCWRELSSAGTRHWRNHVGLRNREKLFFGXMMNEM	60	
	NOV1b	-----MNEM	4	
	Q9UF98	-----	1	
	Q9H7H7	-----	1	
	Q9NRY3	-----	1	
	Q9NY15	-----	1	
20	Q93072	-----	1	
	NOV1a	ERQETGNSKTRYHATAIVQAKHDKGLNKNKGTSGDEEQKIKVGDRDRENKGFGLLDVWNT	120	
	NOV1b	ERQETGNSKTRYHATAIVQAKHDKGLNKNKGTSGDEEQKIKVGDRDRENKGFGLLDVWNT	64	
	Q9UF98	-----	1	
25	Q9H7H7	-----	1	
	Q9NRY3	-----	1	
	Q9NY15	-----	1	
	Q93072	-----	1	
30	NOV1a	LNFIHPCFAVCNVCVHGVCNSGLDGDGTCECYSAYTGPKCDKLTENFHTSHLTLWPVHDSK	180	
	NOV1b	LNFIHPCFAVCNVCVHGVCNSGLDGDGTCECYSAYTGPKCDKLTENFHTSHLTLWPVHDSK	124	
	Q9UF98	-----	1	
	Q9H7H7	-----	1	
	Q9NRY3	-----	1	
35	Q9NY15	-----	1	
	Q93072	-----MA	2	
		-----	1	
40	NOV1a	HWGSLRHQNMNGTCSSGGGKGDPDVYQNGLI FHGGGTSGGLSSSRNRRSSVKRPEKWKGD	240	
	NOV1b	HWGSLRHQNMNGTCSSGGGKGDPDVYQNGLI FHGGGTSGGLSSSRNRRSSVKRPEKWKGD	184	
	Q9UF98	-----	1	

	Q9H7H7	-----	1
	Q9NRY3	-----	1
	Q9NY15	GPRGLLPCLLAFCLAGFSFVRGQVLFKGC DVKTT FVTHVPCTSCAAIKKQTCPSGWLRE	62
	Q93072	-----	1
5	NOV1a	DRDGGGKEGQORRRADTESSLQRGHIKTPLPHRQGEARITETTGN CV SAGMTGTNANH TK	300
	NOV1b	DRDGGGKEGQORRRADTESSLQRGHIKTPLPHRQGEARITETTGN CV SAGMTGTNANH TK	244
	Q9UF98	-----	1
	Q9H7H7	-----	1
10	Q9NRY3	-----	1
	Q9NY15	LPDQITQDCRYEVQLGGSMVSMMSGCRRKCRKQVVQKACCPGYWGSRCHECPGGAETPCNG	122
	Q93072	-----	1
15	NOV1a	VHPTVQSLTEYDSFQTHSTSR LKEFEKQOVKERF-SDPPLMQAIKPSHEKYPPYAQRKGT	359
	NOV1b	VHPTVQSLTEYDSFQTHSTSR LKEFEKQOVKERF-SDPPLMQAIKPSHEKYPPYAQRKGT	303
	Q9UF98	-----	1
	Q9H7H7	-----	1
	Q9NRY3	-----	1
20	Q9NY15	HGTCLDGM DRNGTCVCQENFRGSACQECQDPNRF GPD CQSVCSVHGV CNHGPRGDGSCL	182
	Q93072	-----	1
	NOV1a	SLSPKTQGHGDDEQALLSFLHSITLSLYLYPTTFFHDSPVFIKPGIKTLRLNHFFGSSFP	419
	NOV1b	SLSPKTQGHGDDEQALLSFLHSITLSLYLYPTTFFHDSPVFIKPGIKTLRLNHFFGSSFP	363
	Q9UF98	-----	1
25	Q9H7H7	-----	1
	Q9NRY3	-----	1
	Q9NY15	CFAGYTGP HCDQELPVCQELRCPQNTQCSAEAPSC RCLPGYTQQGSECRAPN---PCWP	238
	Q93072	-----	1
30	NOV1a	YEGSSVIXXMGIEVWKNWCQNADTLAAAPAPSLNVQPCSAQKIPDVRLPLKMKTNWNANA	479
	NOV1b	YEGSSVIXXMGIEVWKNWCQNADTLAAAPAPSLNVQPCSAQKIPDVRLPLKMKTNWNANA	423
	Q9UF98	-----	1
	Q9H7H7	-----	1
	Q9NRY3	-----	1
35	Q9NY15	SPCSLLAQCSVSPKGQAQCHCPENYHGDGMVCLPKDPCTDN-----	279
	Q93072	-----	1
	NOV1a	FPITEAMANTATPSIHVYEKSATLMLIVRTWDQIGTVVHAKKATVGMACACLTWTPAKLT	539
40	NOV1b	FPITEAMANTATPSIHVYEKSATLMLIVRTWDQIGTVVHAKKATVGMACACLTWTPAKLT	483
	Q9UF98	-----	1
	Q9H7H7	-----	1
	Q9NRY3	-----	1
	Q9NY15	---LG--GCPSNSTLCVYQKPGQAFTCTR----PGLVSINSNASAGCFAFCSPFS----	325
45	Q93072	-----	1
	NOV1a	LETALQSLQCANMMGLDRCICQKGYVG DGLTCYGNIMERLRELNTEPRGKWQGRLT SFIS	599
	NOV1b	LETALQSLQCANMMGLDRCICQKGYVG DGLTCYGNIMERLRELNTEPRGKWQGRLT SFIS	543
	Q9UF98	-----	1
	Q9H7H7	-----	1
50	Q9NRY3	-----	1
	Q9NY15	--CDRSATCQVTADGKTSCVCRESEVGDGRACYGHLLHEVQKATQTGRVFLQLRVAVAMM	383
	Q93072	--CDRSATCQVTADGKTSCVCRESEVGDGRACYGHLLHEVQKATQTGRVFLQLRVAVAMM	58
55	NOV1a	LLESIQIVSVQLSEFSQREPTCVNTKSIASNLEGPLVPLSNHYPLQVNELLVDNKAQYF	659
	NOV1b	LLESIQIVSVQLSEFSQREPTCVNTKSIASNLEGPLVPLSNHYPLQVNELLVDNKAQYF	603
	Q9UF98	-----	1
	Q9H7H7	-----	1

	Q9NRY3	-----	1
	Q9NY15	DQGCREILTTAG-PFTVLVPSVSSFSRTMN-ASLAQQLCRQHIIAGQHILEDTRTQQTR	441
	Q93072	DQGCREILTTAG-PFTVLVPSVSSFSRTMN-ASLAQQLCRQHIIAGQHILEDTRTQQTR	116
5	NOV1a	VKLHIIAGQMNI EYMNTDMFYTLTGKSGEIFNSDKDNQIKLKLHGGKKKVKIIQGDIIA	719
	NOV1b	VKLHIIAGQMNI EYMNTDMFYTLTGKSGEIFNSDKDNQIKLKLHGGKKKVKIIQGDIIA	663
	Q9UF98	-----	1
	Q9H7H7	-----	1
	Q9NRY3	-----	1
10	Q9NY15	RWWTLAQEITVTFNQFTKYSYKYKDQPQOTFNIYKANNIAANGVFHVVTGLRWQAPSGT	501
	Q93072	RWWTLAQEITVTFNQFTKYSYKYKDQPQOTFNIYKANNIAANGVFHVVTGLRWQAPSGT	176
	NOV1a	SNGLLHILDDRAMDKLEPTFESNNEETNLGHALDEDGVGGPYTIFVPNNEALNNMKDGTLD	779
	NOV1b	SNGLLHILDDRAMDKLEPTFESNNEETNLGHALDEDGVGGPYTIFVPNNEALNNMKDGTLD	723
15	Q9UF98	-----	1
	Q9H7H7	-----	1
	Q9NRY3	-----	1
	Q9NY15	PGDPKRTIGQILASTEAFSRFETILENCGLPSILDGPG-PFTVFAPSNEAVDSLDRGLI	560
20	Q93072	PGDPKRTIGQILASTEAFSRFETILENCGLPSILDGPG-PFTVFAPSNEAVDSLDRGLI	235
	NOV1a	YLLSP-----ELEVATLISTPHIRSMANQLIQFNTTDNGQILAN--DV	820
	NOV1b	YLLSP-----ELEVATLISTPHIRSMANQLIQFNTTDNGQILAN--DV	764
	Q9UF98	-----	1
	Q9H7H7	-----	1
25	Q9NRY3	-----	1
	Q9NY15	YLFTAGLSKLQELVRYHIYNHGQLTVEKLISKGRILTMANQVLAVNISEEGRILLGPEGV	620
	Q93072	YLFTAGLSKLQELVRYHIYNHGQLTVEKLISKGRILTMANQVLAVNISEEGRILLGPEGV	295
	NOV1a	AMEEIEITAKNGRIYTLTGVLIPPSIVPILPHRCDETKREMKGTCVSCSLVYWSRCPAN	880
30	NOV1b	AMEEIEITAKNGRIYTLTGVLIPPSIVPILPHRCDETKREMKGTCVSCSLVYWSRCPAN	824
	Q9UF98	-----	1
	Q9H7H7	-----	1
	Q9NRY3	-----	1
35	Q9NY15	PLQRVDMVAANGVIHMLD GILLPPTILPILPKHCSEEQHKIVAGSCVDCQALNTSTCPPN	680
	Q93072	PLQRVDMVAANGVIHMLD GILLPPTILPILPKHCSEEQHKIVAGSCVDCQALNTSTCPPN	355
	NOV1a	SEPTALFTHRCVYSGR---FGSLKSGCARYCNATVKCA-----	915
	NOV1b	SEPTALFTHRCVYSGR---FGSLKSGCARYCNATVKCA-----	859
40	Q9UF98	-----	1
	Q9H7H7	-----	1
	Q9NRY3	-----	1
	Q9NY15	SVKLDIFPKECVYIHDPTGLNVLKKGCSYCNQTIMEQGCCKGFFGPDCTQCPGGFSNPC	740
	Q93072	SVKLDIFPKECVYIHDPTGLNVLKKGCSYCNQTIMEQGCCKGFFGPDCTQCPGGFSNPC	415
45	NOV1a	-----DSLGGNGTCICEEGFQGSQCQFCSDPNKYGPRCNKKCLCVHGT CNNRIDSDGA	968
	NOV1b	-----DSLGGNGTCICEEGFQGSQCQFCSDPNKYGPRCNKKCLCVHGT CNNRIDSDGA	912
	Q9UF98	-----	1
	Q9H7H7	-----	1
	Q9NRY3	-----	1
50	Q9NY15	YGKGNCS DGIQNGACL CFPDYKGIACHI CSNPNKHGEQCQEDCGCVHGLCDNRP GSGGV	800
	Q93072	YGKGNCS DGIQNGACL CFPDYKGIACHI CSNPNKHGEQCQEDCGCVHGLCDNRP GSGGV	475
	NOV1a	CLTGTCDRGSAGRLCDKQTSACGPY--VQFCHIHATCEYSNGTASCICKAGYEGDGT LCS	1026
55	NOV1b	CLTGTCDRGSAGRLCDKQTSACGPY--VQFCHIHATCEYSNGTASCICKAGYEGDGT LCS	970
	Q9UF98	-----	1
	Q9H7H7	-----	1
	Q9NRY3	-----	1

	Q9NY15	CQQGTCAPGFSGRFCNESMGDCGPTGLAQHCHLHARCVSQEGVARCRCLDGFEGDGFSC	860
	Q93072	CQQGTCAPGFSGRFCNESMGDCGPTGLAQHCHLHARCVSQEGVARCRCLDGFEGDGFSC	535
5	NOV1a	EMDPCTGLTPGGCSRNAECIKTGTGTHTCVCQQGWTGNRDCSEINNCLLPSAGGCHDNA	1086
	NOV1b	EMDPCTGLTPGGCSRNAECIKTGTGTHTCVCQQGWTGNRDCSEINNCLLPSAGGCHDNA	1030
	Q9UF98	-----	1
	Q9H7H7	-----	1
	Q9NRY3	-----	1
10	Q9NY15	PSNPCSHPDRCGGCSENAECVPGSLGTHHCTCHKGWSGDGRVCVAIDECELDVGGGCHTDA	920
	Q93072	PSNPCSHPDRCGGCSENAECVPGSLGTHHCTCHKGWSGDGRVCVAIDECELDVGGGCHTDA	595
	NOV1a	SCLYVGPQGNECECKKGFRNGIDCEPITSCLEQTGKCHPLASCQSTSSGVWSCVCQEGY	1146
	NOV1b	SCLYVGPQGNECECKKGFRNGIDCEPITSCLEQTGKCHPLASCQSTSSGVWSCVCQEGY	1090
	Q9UF98	-----	1
15	Q9H7H7	-----	1
	Q9NRY3	-----	1
	Q9NY15	LCSYVGPQGSRCTCKLGFAGDGYQCSPIDPCRAGNGGCHGLATCRAVGGGQRVCTCPPGF	980
	Q93072	LCSYVGPQGSRCTCKLGFAGDGYQCSPIDPCRAGNGGCHGL-----	636
20	NOV1a	EGDGFCLCYGNAAVELSFLSEAAIFNRWINNASLQPTLSATSNLTVLVPSQQATEDMDQDE	1206
	NOV1b	EGDGFCLCYGNAAVELSFLSEAAIFNRWINNASLQPTLSATSNLTVLVPSQQATEDMDQDE	1150
	Q9UF98	-----	1
	Q9H7H7	-----	1
	Q9NRY3	-----	1
25	Q9NY15	GGDGFSCYGDIFRELEANAHFSIFYQWLKSAG--ITLPADRRVTALVPSEAAVRQLSPED	1038
	Q93072	-----ELEANAHFSIFYQWLKSAG--ITLPADRRVTALVPSEAAVRQLSPED	681
	NOV1a	KSFWLSQSNIPALIKYHMLLGTyrVADLQTLSSSDMLATSLQGNFLHLAKVDGNITIEGA	1266
30	NOV1b	KSFWLSQSNIPALIKYHMLLGTyrVADLQTLSSSDMLATSLQGNFLHLAKVDGNITIEGA	1210
	Q9UF98	-----	1
	Q9H7H7	-----	1
	Q9NRY3	-----	1
	Q9NY15	RAFWLQPRTLPNLVRAHFLQALFEEELARLGGQE-VATLNPTRWEIRNISGRVWVQNA	1097
35	Q93072	RAFWLQPRTLPNLVRAHFLQALFEEELARLGGQE-VATLNPTRWEIRNISGRVWVQNA	740
	NOV1a	SIVDGDNAATNGVIHIINKVLVPQRRLTGSLPNLLMRLEQMPDYSIFRGYIIQYNLANAI	1326
	NOV1b	SIVDGDNAATNGVIHIINKVLVPQRRLTGSLPNLLMRLEQMPDYSIFRGYIIQYNLANAI	1270
	Q9UF98	-----	1
	Q9H7H7	-----	1
40	Q9NRY3	-----	1
	Q9NY15	SVDVADLLATNGVLHILSQVLLPGRGDVPGGQGLLQQLDLVPAFSLFRELLQHHGLVPQI	1157
	Q93072	SVDVADLLATNGVLHILSQVLLPGRGDVPGGQGLLQQLDLVPAFSLFRELLQHHGLVPQI	800
45	NOV1a	EAADAYTVFAPNNNAIENYIREKKVLSLEEDVLRyhVVLEEKLLKNDLHNGMHRETMLGF	1386
	NOV1b	EAADAYTVFAPNNNAIENYIREKKVLSLEEDVLRyhVVLEEKLLKNDLHNGMHRETMLGF	1330
	Q9UF98	-----	1
	Q9H7H7	-----	1
	Q9NRY3	-----	1
50	Q9NY15	EAATAYTIFVPTNRSLEAQ---GNSSHLADTVRHHVVLGEALSMETLRKGHRNSLLGP	1214
	Q93072	EAATAYTIFVPTNRSLEAQ---GNSSHLADTVRHHVVLGEALSMETLRKGHRNSLLGP	857
	NOV1a	SYFLSFFLHNDQLYVNEAPINYTNVATDKGVHGLGKVLLEIQKNRCDNNDTTIIRGRCRT	1446
55	NOV1b	SYFLSFFLHNDQLYVNEAPINYTNVATDKGVHGLGKVLLEIQKNRCDNNDTTIIRGRCRT	1390
	Q9UF98	-----	1
	Q9H7H7	-----	1
	Q9NRY3	-----	1
	Q9NY15	AHWIVFYNHSGQPEVNHVPLEGPMLEAPGRSLIGLSGVLTVGSSRCLHSHAEALREKCVN	1274

	Q93072	AHWIVFYNHSGQPEVNVHPLEGPMLEAPGRSLIGLSGVLTGSSRCLHSHAEALREKCVN	917
	NOV1a	CSSELTCPFGTKSLGNEKRRCIYTSYFMGRRTLFIGCQPKCVRTVITRECCAGFFGPQCQ	1506
	NOV1b	CSSELTCPFGTKSLGNEKRRCIYTSYFMGRRTLFIGCQPKCVRTVITRECCAGFFGPQCQ	1450
5	Q9UF98	-----	1
	Q9H7H7	-----	1
	Q9NRY3	-----	1
	Q9NY15	CTRRFRCTQGFQLQDTPRKSCVYRSGFSFSR----GCSYTCAKKIQVPDCCPGFFGTLC	1330
10	Q93072	CTRRFRCTQGFQLQDTPRKSCVYRSGFSFSR----GCSYTCAKKIQVPDCCPGFFGTLC	973
	NOV1a	PCPGNAQNVCFGNGICLDGVNGTGVCECGEGFSGTACETCTEGKYGIHCDQACSCVHGRC	1566
	NOV1b	PCPGNAQNVCFGNGICLDGVNGTGVCECGEGFSGTACETCTEGKYGIHCDQACSCVHGRC	1510
	Q9UF98	-----	1
	Q9H7H7	-----WHLFGWSDGTGVCECGEGFSGTACETCTEGKYGIHCDQACSCVHGRC	47
15	Q9NRY3	-----	1
	Q9NY15	PCPGGLGGVCSGHGQCQDRFLGSGECHCHEGFHGTACEVCELGRYPNCTGVCDCAHGLC	1390
	Q93072	PCPGGLGGVCSGHGQCQDRFLGSGECHCHEGFHGTACEVCELGRYPNCTGVCDCAHGLC	1033
	NOV1a	NQGPLGDGSCDCDVGWRGVHCDNATTEDNCNGTCHTSANCLTNSDGTASCKCAAGFQNG	1626
20	NOV1b	NQGPLGDGSCDCDVGWRGVHCDNATTEDNCNGTCHTSANCLTNSDGTASCKCAAGFQNG	1570
	Q9UF98	-----VGEAVGTASCKCAAGFQNG	20
	Q9H7H7	NQGPLGDGSCDCDVGWRGVHCDNATTEDNCNGTCHTSANCLTNSDGTASCKCAAGFQNG	107
	Q9NRY3	-----	1
	Q9NY15	QEGLOGDGSCVCNVGWQGLRCDQKITSPOCPRKCDPNANCVQDSAGASTCACAAGYSNG	1450
25	Q93072	QEGLOGDGSCVCNVGWQGLRCDQKITSPOCPRKCDPNANCVQDSAGASTCACAAGYSNG	1093
	NOV1a	TICTAINACEISNGGCSAKADCKRTTPGRRVCTCKAGYTGDIIVCLEINPCLENHGGCDK	1686
	NOV1b	TICTAINACEISNGGCSAKADCKRTTPGRRVCTCKAGYTGDIIVCLEINPCLENHGGCDK	1630
	Q9UF98	TICTAINACEISNGGCSAKADCKRTTPGRRVCTCKAGYTGDIIVCLEINPCLENHGGCDK	80
30	Q9H7H7	TICTAINACEISNGGCSAKADCKRTTPGRRVCTCKAGYTGDIIVCLEINPCLENHGGCDK	167
	Q9NRY3	-----	1
	Q9NY15	IFCSEVDPCAHHGGCSPHANCTKVAPGORTCTCQDGYMGDGLCQEINSCLIHGGCHI	1510
	Q93072	IFCSEVDPCAHHGGCSPHANCTKVAPGORTCTCQDGYMGDGLCQEINSCLIHGGCHI	1153
	NOV1a	NAECTQTGPNQAACNCLPAYTGDGK-VCTLINVCLTKNGGCSEFAICNHTGQVERTCTCK	1745
35	NOV1b	NAECTQTGPNQAACNCLPAYTGDGK-VCTLINVCLTKNGGCSEFAICNHTGQVERTCTCK	1689
	Q9UF98	NAECTQTGPNQAACNCLPAYTGDGK-VCTLINVCLTKNGGCSEFAICNHTGQVERTCTCK	139
	Q9H7H7	NAECTQTGPNQAACNCLPAYTGDGK-VCTLINVCLTKNGGCSEFAICNHTGQVERTCTCK	226
	Q9NRY3	-----	1
40	Q9NY15	HAECIPTGPQQVSCSCREGYSGDGIRTCELLDPCSKNNGGCSPYATCKSTGDGQRTCTCD	1570
	Q93072	HAECIPTGPQQVSCSCREGYSGDGIRTCELLDPCSKNNGGCSPYATCKSTGDGQRTCTCD	1213
	NOV1a	PNY-IGDGFTCRGSIYQELPKNPKTSQYFFQLQEHFVKDLVGPFPFTVFAPLSAAFDEEA	1804
	NOV1b	PNY-IGDGFTCRGSIYQELPKNPKTSQYFFQLQEHFVKDLVGPFPFTVFAPLSAAFDEEA	1748
45	Q9UF98	PNY-IGDGFTCRGSIYQELPKNPKTSQYFFQLQEHFVKDLVGPFPFTVFAPLSAAFDEEA	198
	Q9H7H7	PNY-IGDGFTCRGSIYQELPKNPKTSQYFFQLQEHFVKDLVGPFPFTVFAPLSAAFDEEA	285
	Q9NRY3	-----	1
	Q9NY15	TAHTVGDGLTCCRARVGLLELLRDKHAS--FFSLRLLEYKELKGDGPFTIFVPHADLMSNLS	1628
	Q93072	TAHTVGDGLTCCRARVGLLELLRDKHAS--FFSLRLLEYKELKGDGPFTIFVPHADLMSNLS	1271
50			
	NOV1a	RVKDWDKYGLMPQVRLRYHVVACHQLLLENLKLISNATSLQGEPIVISVSQSTVYINNKA	1864
	NOV1b	RVKDWDKYGLMPQVRLRYHVVACHQLLLENLKLISNATSLQGEPIVISVSQSTVYINNKA	1808
	Q9UF98	RVKDWDKYGLMPQVRLRYHVVACHQLLLENLKLISNATSLQGEPIVISVSQSTVYINNKA	258
	Q9H7H7	RVKDWDKYGLMPQVRLRYHVVACHQLLLENLKLISNATSLQGEPIVISVSQSTVYINNKA	345
55	Q9NRY3	-----MPQVRLRYHVVACHQLLLENLKLISNATSLQGEPIVISVSQSTVYINNKA	50
	Q9NY15	QDELARIRAHRLVFRYHVVGCRRLRSEDILLEQGYATALS GHPLRFSEREGSIYLNDFAR	1688
	Q93072	QDELARIRAHRLVFRYHVVGCRRLRSEDILLEQGYATALS GHPLRFSEREGSIYLNDFAR	1331

5	NOV1a	IISDDIISTNGIVHIIDKLLSPKNLLITPKDNSGRILQNLTTLATNNGYIKFSNLIQDSG	1924
	NOV1b	IISDDIISTNGIVHIIDKLLSPKNLLITPKDNSGRILQNLTTLATNNGYIKFSNLIQDSG	1868
	Q9UF98	IISDDIISTNGIVHIIDKLLSPKNLLITPKDNSGRILQNLTTLATNNGYIKFSNLIQDSG	318
	Q9H7H7	IISDDIISTNGIVHIIDKLLSPKNLLITPKDNSGRILQNLTTLATNNGYIKFSNLIQDSG	405
	Q9NRY3	IISDDIISTNGIVHIIDKLLSPKNLLITPKDNSGRILQNLTTLATNNGYIKFSNLIQDSG	110
10	Q9NY15	VVSSDHEAVNGILHFIDRVLLPPEALHWEPPDAPIPRRNVTAQAQGGFGYKIFSGILKVGAG	1748
	Q93072	VVSSDHEAVNGILHFIDRVLLPPEALHWEPPDAPIPRRNVTAQAQGGFGYKIFSGILKVGAG	1391
15	NOV1a	LLSVITDPIHTPVTLFWPTDQALH---ALPAEQDQDFLFDQDNKDKLKEYLKFHVIRDAKV	1981
	NOV1b	LLSVITDPIHTPVTLFWPTDQALHALHALPAEQDQDFLFDQDNKDKLKEYLKFHVIRDAKV	1928
	Q9UF98	LLSVITDPIHTPVTLFWPTDQALH---ALPAEQDQDFLFDQDNKDKLKEYLKFHVIRDAKV	375
	Q9H7H7	LLSVITDPIHTPVTLFWPTDQALH---ALPAEQDQDFLFDQDNKDKLKEYLKFHVIRDAKV	462
	Q9NRY3	LLSVITDPIHTPVTLFWPTDQALH---ALPAEQDQDFLFDQDNKDKLKEYLKFHVIRDAKV	167
20	Q9NY15	LLPLLREASHRPFTMLWPTDAAFR---ALPPDRQAWLYHEDHRDKLAAILRGHMIRNVEA	1805
	Q93072	LLPLLREASHRPFTMLWPTDAAFR---ALPPDRQAWLYHEDHRDKLAAILRGHMIRNVEA	1448
25	NOV1a	LAVDLPTSTAWKTLOGSELSVKCGAGRDIGDLFLNGQTCRIVQRELLFDLGVAYGIDCLL	2041
	NOV1b	LAVDLPTSTAWKTLOGSELSVKCGAGRDIGDLFLNGQTCRIVQRELLFDLGVAYGIDCLL	1988
	Q9UF98	LAVDLPTSTAWKTLOGSELSVKCGAGRDIGDLFLNGQTCRIVQRELLFDLGVAYGIDCLL	435
	Q9H7H7	LAVDLPTSTAWKTLOGSELSVKCGAGRDIGDLFLNGQTCRIVQRELLFDLGVAYGIDCLL	522
	Q9NRY3	LAVDLPTSTAWKTLOGSELSVKCGAGRDIGDLFLNGQTCRIVQRELLFDLGVAYGIDCLL	227
30	Q9NY15	LASDLPLNLGPLRTMHGTPISFSQSRTR-PGELMVGEDDARIVORHLPEEGGLAYGIDQLL	1864
	Q93072	LASDLPLNLGPLRTMHGTPISFSQSRTR-PGELMVGEDDARIVORHLPEEGGLAYGIDQLL	1507
35	NOV1a	IDPTLGGRCDTFTTFDASG-ECGSCVNTSPSCRWSKPKGVKQKCLYNLP-----	2089
	NOV1b	IDPTLGGRCDTFTTFDASG-ECGSCVNTSPSCRWSKPKGVKQKCLYNLP-----	2036
	Q9UF98	IDPTLGGRCDTFTTFDASG-ECGSCVNTSPSCRWSKPKGVKQKCLYNLP-----	483
	Q9H7H7	IDPTLGGRCDTFTTFDASG-ECGSCVNTSPSCRWSKPKGVKQKCLYNLP-----	570
	Q9NRY3	IDPTLGGRCDTFTTFDASG-ECGSCVNTSPSCRWSKPKGVKQKCLYNLP-----	275
40	Q9NY15	EPPGLGARCDHFEETRPLRLNTCSICGLEPPCPGEGSQEQQSPEACWRFFPKFWTSPPLHSL	1924
	Q93072	EPPGLGARCDHFEETRPLRLNTCSICGLEPPCPGEGSQEQQSPEACWRFFPKFWTSPPLHSL	1567
45	NOV1a	-----FKRNLEG-----CRERCSLVIQIPRCCKGYFGRDCQACPGGPDAPCNRGV	2135
	NOV1b	-----FKRNLEG-----CRERCSLVIQIPRCCKGYFGRDCQACPGGPDAPCNRGV	2082
	Q9UF98	-----FKRNLEG-----CRERCSLVIQIPRCCKGYFGRDCQACPGGPDAPCNRGV	529
	Q9H7H7	-----FKRNLEG-----CRERCSLVIQIPRCCKGYFGRDCQACPGGPDAPCNRGV	616
	Q9NRY3	-----FKRNLEG-----CRERCSLVIQIPRCCKGYFGRDCQACPGGPDAPCNRGV	321
50	Q9NY15	GLRSVWVHPSLWGRPQGLGRGCHRNCTTTTWKPSCCPGHYGSECCQACPGGSSPCSDRGV	1984
	Q93072	GLRSVWVHPSLWGRPQGLGRGCHRNCTTTTWKPSCCPGHYGSECCQACPGGSSPCSDRGV	1627
55	NOV1a	CLDQYSATGECKCNTGFNGTACEMCWPGRFPGDCLPCGCSDHGQCDDGITGSGQCLCETG	2195
	NOV1b	CLDQYSATGECKCNTGFNGTACEMCWPGRFPGDCLPCGCSDHGQCDDGITGSGQCLCETG	2142
	Q9UF98	CLDQYSATGECKCNTGFNGTACEMCWPGRFPGDCLPCGCSDHGQCDDGITGSGQCLCETG	589
	Q9H7H7	CLDQYSATGECKCNTGFNGTACEMCWPGRFPGDCLPCGCSDHGQCDDGITGSGQCLCETG	676
	Q9NRY3	CLDQYSATGECKCNTGFNGTACEMCWPGRFPGDCLPCGCSDHGQCDDGITGSGQCLCETG	381
55	Q9NY15	CMGMSGSGQCLCRSGFAGTACELCAPGAFGPHCQACRCIVHGRCDGELGSGSGCFCDG	2044
	Q93072	CMGMSGSGQCLCRSGFAGTACELCAPGAFGPHCQACRCIVHGRCDGELGSGSGCFCDG	1687
55	NOV1a	WTGPSCDTQAVLPAVCTPPCSAHATCKENNTCECNLDYEGDGITCTVVDFFCKQDNGGCAK	2255
	NOV1b	WTGPSCDTQAVLPAVCTPPCSAHATCKENNTCECNLDYEGDGITCTVVDFFCKQDNGGCAK	2202
	Q9UF98	WTGPSCDTQAVLPAVCTPPCSAHATCKENNTCECNLDYEGDGITCTVVDFFCKQDNGGCAK	649
	Q9H7H7	WTGPSCDTQAVLPAVCTPPCSAHATCKENNTCECNLDYEGDGITCTVVDFFCKQDNGGCAK	736
	Q9NRY3	WTGPSCDTQAVLPAVCTPPCSAHATCKENNTCECNLDYEGDGITCTVVDFFCKQDNGGCAK	441
55	Q9NY15	WTGPRCEVQLELQPVCTPPCAPEAVCRAGNSCECSLGYEGDGRVCTVADLQDGHGGCSE	2104
	Q93072	WTGPRCEVQLELQPVCTPPCAPEAVCRAGNSCECSLGYEGDGRVCTVADLQDGHGGCSE	1747

	NOV1a	VARCSQKGTKVSCSCQKGYKGDGHSCTEIDPCADGLNGGCHEHATCKMTGPGKHKCECKS	2315
	NOV1b	VARCSQKGTKVSCSCQKGYKGDGHSCTEIDPCADGLNGGCHEHATCKMTGPGKHKCECKS	2262
	Q9UF98	VARCSQKGTKVSCSCQKGYKGDGHSCTEIDPCADGLNGGCHEHATCKMTGPGKHKCECKS	709
	Q9H7H7	VARCSQKGTKVSCSCQKGYKGDGHSCTEIDPCADGLNGGCHEHATCKMTGPGKHKCECKS	796
5	Q9NRY3	VARCSQKGTKVSCSCQKGYKGDGHSCTEIDPCADGLNGGCHEHATCKMTGPGKHKCECKS	501
	Q9NY15	HANCSQVGTMTCTCTCLPDYEGDGWSCRARNPCTDGHRRGCSEHANCLSTGLNTRRCECHA	2164
	Q93072	HANCSQVGTMTCTCTCLPDYEGDGWSCRARNPCTDGHRRGCSEHANCLSTGLNTRRCECHA	1807
	NOV1a	HYVGDLNCEPE-QLPIDRCLQDNGQCHADAKCVDLHFQDITVGVFHLRSPLGQYKLTFD	2374
10	NOV1b	HYVGDLNCEPE-QLPIDRCLQDNGQCHADAKCVDLHFQDITVGVFHLRSPLGQYKLTFD	2321
	Q9UF98	HYVGDLNCEPE-QLPIDRCLQDNGQCHADAKCVDLHFQDITVGVFHLRSPLGQYKLTFD	768
	Q9H7H7	HYVGDLNCEPE-QLPIDRCLQDNGQCHADAKCVDLHFQDITVGVFHLRSPLGQYKLTFD	855
	Q9NRY3	HYVGDLNCEPE-QLPIDRCLQDNGQCHADAKCVDLHFQDITVGVFHLRSPLGQYKLTFD	560
	Q9NY15	GYVGDLQCLEESEPVDRCLGQPPPCHS DAMCTDQHFQEKRAGVFHLQATSGPYGLNFS	2224
15	Q93072	GYVGDLQCLEESEPVDRCLGQPPPCHS DAMCTDQHFQEKRAGVFHLQATSGPYGLNFS	1867
	NOV1a	KAREACANEATMATYNQLSYAQKAKYHLCSAGWLETGRVAYPTAFASQNCGSGVVGIVD	2434
	NOV1b	KAREACANEATMATYNQLSYAQKAKYHLCSAGWLETGRVAYPTAFASQNCGSGVVGIVD	2381
	Q9UF98	KAREACANEATMATYNQLSYAQKAKYHLCSAGWLETGRVAYPTAFASQNCGSGVVGIVD	828
20	Q9H7H7	KAREACANEATMATYNQLSYAQKAKYHLCSAGWLETGRVAYPTAFASQNCGSGVVGIVD	915
	Q9NRY3	KAREACANEATMATYNQLSYAQKAKYHLCSAGWLETGRVAYPTAFASQNCGSGVVGIVD	620
	Q9NY15	EAEAAACEAQAVALASEPQLSAAQQLGFHLCLMGWLANGSTAHPVVFVPVADCCNGRVGVVS	2284
	Q93072	EAEAAACEAQAVALASEPQLSAAQQLGFHLCLMGWLANGSTAHPVVFVPVADCCNGRVGVVS	1927
25	NOV1a	YGPRPNKSEMWDVFCYRMKEVLAYSNS SARGRAFLEHLTDL SIRGTLFVPQNSGLGENET	2494
	NOV1b	YGPRPNKSEMWDVFCYRMKG-----	2401
	Q9UF98	YGPRPNKSEMWDVFCYRMK-----G-----	848
	Q9H7H7	YGPRPNKSEMWDVFCYRMKDVNCTCKVGYVGDGF-----	949
	Q9NRY3	YGPRPNKSEMWDVFCYRMKDVNCTCKVGYVGDGF-----	654
30	Q9NY15	LGARKNLSEKWDAYCERFVQDVACRCRNGFVGDG-----	2317
	Q93072	LGARKNLSEKWDAYCERFVQDVACRCRNGFVGDG-----	1960
	NOV1a	LSGRDIEHHLANVSMFFYNDLVNGTTLQTRLGSKLLIT-----AS	2534
35	NOV1b	-----SAG--LFQQ-----LSSRPCIS-----RT	2418
	Q9UF98	-----SAG--LFQQ-----LSSRPCIS-----RT	865
	Q9H7H7	-----SCSGNLLQV-----LMSFPSLTNFLTTEVLAYSNS SARGRAFLEH	988
	Q9NRY3	-----SCSGNLLQV-----LMSFPSLTNFLTTEVLAYSNS SARGRAFLEH	693
	Q9NY15	-----ISTCNGKLLDV-----LAATANFSTFYGMMLGYANATQRGDLDFLDF	2358
40	Q93072	-----ISTCNGKLLDV-----LAATANFSTFYGMMLGYANATQRGDLDFLDF	2001
	NOV1a	QDPLQPVQSRFVDGRAILQWDIFASNGIIHVISRPLKAPPAPVTLTHTGLGAGIFFCIIL	2594
	NOV1b	PD-----	2420
	Q9UF98	PDDL SIRGTLFVPQNSGLGENETLSGRDIEHHLANVSMFFYNDLVNGTTLQTRLGSKLLI	925
45	Q9H7H7	LTDLSIRGTLFVPQNSGLGENETLSGRDIEHHLANVSMFFYNDLVNGTTLQTRLGSKLLI	1048
	Q9NRY3	LTDLSIRGTLFVPQNSGLGENETLSGRDIEHHLANVSMFFYNDLVNGTTLQTRVGSKLLI	753
	Q9NY15	LDELTYKTLFVPVNEGFVDNMTLSGPDLELHASNATLLSAN-ASQKLLPAHSGLSLII	2417
	Q93072	LDELTYKTLFVPVNEGFVDNMTLSGPDLELHASNATLLSAN-ASQKLLPAHSGLSLII	2060
	NOV1a	VTG---AVALAAYSIFRINRRTIGYQHFESEEDINVAALGKQOPENIS-----NPLYEST	2646
50	NOV1b	-----	2420
	Q9UF98	TAS---QDPLQPTETRFVDGRAILQWDIFASNGIIHVISRPLKAPPAP-----VTLTHTG	977
	Q9H7H7	TAS---QDPLQPTETRFVDGRAILQWDIFASNGIIHVISRPLKAPPAP-----VTLTHTG	1100
	Q9NRY3	TAS---QDPLQPTETRFVDGRAILQWDIFASNGIIHVISRPLKAPPAP-----VTLTHTG	805
	Q9NY15	SDAGPDNSSWAPVAPGTVVVSRIIVWDIMAFNGIIHALASPLLAPPQPQAVLAPEAPPVA	2477
55	Q93072	SDAGPDNSSWAPVAPGTVVVSRIIVWDIMAFNGIIHALASPLLAPPQPQAVLAPEAPPVA	2119
	NOV1a	TSAPPEPSYDPFTDSEERQLEGNDPLRTL-----	2675

NOV1b	-----	2420
Q9UF98	LGAGIFFAIILVTGAVALAAYSIFRINRRTIGFQHFSEEDINVAALGKQQPENISNPLY	1037
Q9H7H7	LGAGIFFAIILVTGAVALAAYSIFRINRRTIGFQHFSEEDINVAALGKQQPENISNPLY	1160
Q9NRY3	LGAGIFFAIILVTGAVALAAYSIFRINRRTIGFQHFSEEDINVAALGKQQPENISNPLY	865
Q9NY15	AGVGAVLAAGALLGLVAGALYLRARGKPTGFGFSAFQAEDDADDDFSPWQEGTNPTLVSV	2537
Q93072	AGVGAVLAAGALLGLVAGALYLRARGKPMGFGFSAFQAEDDADDDFSPWQEGTNPTLVSV	2179
NOV1a	-----	2675
NOV1b	-----	2420
Q9UF98	ESTTSAPPEPSYDPFTDSEERQLEGNDPLRTL-	1069
Q9H7H7	ESTTSAPPEPSYDPFTDSEERQLEGNDPLRTL-	1192
Q9NRY3	ESTTSAPPEPSYDPFTDSEERQLEGNDPLRTL-	897
Q9NY15	PNPVFGSDTFCEPFDDSLLEEDFPDTQRILT VK	2570
Q93072	PNPVFGSDTFCEPFDDSLLEEDFPDTQRILT VK	2212

Domain results for NOV1 were collected from the Pfam database, and then identified by the InterPro domain accession number. The results are listed in Table 1K with the statistics and domain description. These results indicate that the NOV1 polypeptides have properties similar to those of other proteins known to contain these domains.

Table 1K. Domain Analysis of NOV1		
PSSMs Producing Significant Alignments	Score (bits)	E Value
Fasciclin; domain 3 of 4, from 1756 to 1886	53.1	6.3e-12
Fasciclin	agtvmeklkt dprfstlvaaleaadLvetlnnsgdfTVFAPTNDaFq	
NOV1a	+++ + ++ + +++ +++++ +++++ + + RGSIIYQELPKNPKTSQYFFQLQEH-FVKDLVGP GPFTVFAPLSAAFD	
NOV1a	kLpagdlktldeLlnkedakqLakILtYH.Vvagklstadllslstpvlt +++ +++ + ++ + +++ ++ ++ + E-EAR---VKDWDKY---GLMPQVLRyHvVACHQLLENLKLISN--AT	
NOV1a	slqGskitvsgkndtellkdvnvlkVnnatvivesDiettnGviHviDrV +++ +++ +++++ + + ++ + +++++ + ++ ++ ++ ++ SLQGEPIVISVSQST-----VYINNKAIISSDIISTNGIVHIIDKL	
NOV1a	LLP (SEQ ID NO:44) LSP (SEQ ID NO:2)	
Fasciclin; domain 4 of 4, from 1900 to 2043	41.9	1.5e-08
Fasciclin	agtvmeklkt dprfstlvaaleaadLvetlnnsg..dfTVFAPTNDa	
NOV1a	++++++ +++ +++ ++ +++ +++ +++++ + + ILQNLTTLATNNGYIKFSNLIQDSGLLSVITDPIhtPVTLEFWPTDQA	

NOV1a	FqkLpagdlktldeLlnkedakqLakILtYHVvagklstadllslstpv1 + + +++ ++ ++++++ ++ ++ + + ++ + +++++ LHALPAE---QQDFLFNQDNKDKLKEYLKFHVIRDAKVLAVDLPTSTA-W
NOV1a	tslqGskitvsgkndtellkdvnvlkVnnat.vivesDietNGviHViD ++++ ++++++ ++ ++ + ++ + +++ + + + + + KTLQGSELSVKCGAGR---DIGDLFLNGQTcRIVQRELLFDLGVAYGID
NOV1a	rVLlP (SEQ ID NO:45) + CLLID (SEQ ID NO:2)
Xlink: domain 1 of 1, from 2358 to 2450	
Xlink	GeVFhyrapsgRYkltFeEAqaaClrqqAriATtgQLyAAwkgGfdq + +++++ + +++ + +++ +++ + + ++ ++ NOV1a -GVFHLRSPLGQYKLTFDKAREACANEAATMATYNQLSYAQKAKYHL
NOV1a	CdAGWLADgsVRYPIvkPrenCgGdkdgifpGVRtyYlfpNQTGFpddpss + ++ +++ + + + ++ +++++ CSAGWLETGRVAYPTAFASQNCGSgv---VGIVDY-----GPRPNKSE
NOV1a	rYDvYCF (SEQ ID NO:46) + ++ + MWDVFCY (SEQ ID NO:2)

The NOV1 proteins disclosed in this invention is expressed in at least the following tissues: adrenal gland, bone marrow, brain - amygdala, brain - cerebellum, brain - hippocampus, brain - substantia nigra, brain - thalamus, brain - whole, fetal brain, fetal kidney, fetal liver, fetal lung, heart, kidney, lymphoma - Raji, mammary gland, pancreas, pituitary gland, placenta, prostate, salivary gland, skeletal muscle, small intestine, spinal cord, spleen, stomach, testis, thyroid, trachea and uterus. This information was derived by determining the tissue sources of the sequences that were included in the invention including but not limited to SeqCalling sources, Public EST sources, Literature sources, and/or RACE sources.

The protein similarity information, expression pattern, cellular localization, and map location for the NOV1 proteins and nucleic acids disclosed herein suggest that this Stabilin-like protein may have important structural and/or physiological functions characteristic of the Stabilin and/or epidermal growth factor (EGF) families. Therefore, the nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications. For example, the compositions of the present invention will have efficacy for treatment of patients suffering from: heart diseases (particularly mechanisms of angiogenesis), cancers such as, for example, erythroid-megakaryocytic leukaemia, breast cancer, fibrosarcoma, neoplasia, such as T-cell acute

lymphoblastic leukemia/lymphoma and mammary carcinomas, chronic contact dermatitis, familial and congenital cholestatic diseases, Hereditary vascular dementia, neurological diseases, CNS disorders, autoimmune disease, inflammation, immunodeficiencies, systemic lupus erythematosus, metabolic disorders (obesity and/or diabetes), asthma, emphysema, scleroderma, allergies, and other diseases, disorders and conditions of the like.

The novel nucleic acid encoding the Stabilin/Fascin-like protein of the invention, or fragments thereof, are useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed. These materials are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. The disclosed NOV1 protein has multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, a contemplated NOV1 epitope is from about amino acids 45 to 125. In another embodiment, a contemplated NOV1 epitope is from about amino acids 200 to 375. In other specific embodiments, contemplated NOV1 epitopes are from about amino acids 400 to 2700.

NOV2

Another NOVX protein of the invention, referred to herein as NOV2, includes two novel polydom-like proteins. The disclosed proteins have been named NOV2a and NOV2b. Polydom-like proteins are important for the regulation of hematopoiesis and may play a role in cell adhesion or in the immune system. Domains within this protein have been shown to be important in coagulation, growth, cell division, and other important cellular processes.

Although some members of the polydom-like protein family may be localized in the lysosome, the protein predicted here is similar to the mouse polydom protein which is localized extracellularly. Therefore, it is likely that this polydom-like protein is available at the same localization, and hence accessible to a diagnostic probe, and for the various therapeutic applications described herein.

The NOV2a and NOV2b proteins disclosed in this invention map to chromosome 9. This information was assigned using OMIM, the electronic northern bioinformatic tool implemented

by CuraGen Corporation, public ESTs, public literature references and/or genomic clone homologies.

NOV2a

5 In one embodiment, a NOV2 variant is NOV2a (alternatively referred to herein as CG142106342), which encodes a novel polydom-like protein and includes the 11158 nucleotide sequence (SEQ ID NO:5) shown in Table 2A. An open reading frame for the mature protein was identified beginning with an ATG codon at nucleotides 77-79 and ending with a TAA codon at nucleotides 10787-10789. Putative untranslated regions downstream from the termination codon and upstream from the initiation codon are underlined in Table 2A, and the start and stop codons are in bold letters.

Table 2A. NOV2a Nucleotide Sequence (SEQ ID NO:5)

CAATTGGTCTAGGGTCTCCCCCATTGGAATATCCATCAGTGATGAGAAATACAACGTTTGTGAGTTTCTCTAGC
ATGAGAAGAATTTGCGCGGCTTGCTGGGGTCTGGCGCTCGTTTCGGGCTGGGCGACCTTTCAGCAGATGTCCCCGT
CGCGCAATTTTCAGCTTCCGCCTCTTCCCCGAGACCGCGCCCGGGGCCCCGGGAGTATCCCCGCGCCGCCGCTCC
TGGCGACGAAGCGGCGGGGAGCAGAGTGGAGCGGCTGGGCCAGGCGTTCGCGTGCGGCTGCTGCGGGAGCTCAGC
GAGCGCCTGGAGCTTGTCTTCTGGTGGATGATTCTGCCAGCGTGGGCGAAGTCAACTTCCGCGAGCGAGCTCATGT
TCGTCCGCAAGCTGCTGTCCGACTTCCCCGTGGTGGCCACGGCCACGCGCGTGGCCATCGTGACCTTCTCGTCCAA
GAACTACGTGGTGCCGCGCTCGATTACATCTCCACCCGCGCGCGCGCCAGCACAAAGTGCGCGCTGCTCCTCCAA
GAGATCCCTGCCATCTCTACCGAGGTGGCGGCACCTACACCAAGGGCGCCTTCCAGCAAGCCGCGCAAATCTCTC
TTTCATGCTAGAGAAACTCAACAAAAGTTGTATTTCTCATCACTGATGGATATTCCAATGGGGGAGACCTTAGACC
AATTGCAGCGTCACTGCGAGATTCAAGAGTGGAGATCTTCACTTTTGGCATATGGCAAGGGAACATTTCGAGAGCTG
AATGACATGGCTTCCACCCCAAAGGAGGAGCACTGTTACCTGCTACACAGTTTGAAGAATTTGAGGCTTTAGTCG
CCCTCTGTTCATATGTTATTTGTAGATCTACCTTCTGGGAGTTTATTCAAGATGATATGGTCCACTGCTCATATCT
TTGTGATGAAGGCAAGGACTGCTGTGACCGAATGGGAAGCTGCAATGTGGGAAACACACAGGCCATTTTGAGTGC
ATCTGTGAAAAGGGGTATAACGGGAAAGGTCTGCAGTATGACTGCACAGTTTGGCCATCGGGGACATACAAACCTG
AAGGCTCACCAGGAGGAATCAGCAGTTGCATTCCATGTCTGATGAAAATCACACCTCTCCACCTGGAAGCACATC
CCCTGAAGACTGTGTCTGCAGAGAGGGATACAGGGCATCTGGCCAGACCTGTGAAGTTGTCCACTGCCCTGCCCTG
AAGCTCCCCGAAAATGGTTACTTTATCCAAAACACTTGCAACAACCACTTCAATGCAGCCTGTGGGGTCCGATGTC
ACCCTGGATTTGATCTTGTGGGAAGCAGCATCATCTATGTCTACCCAATGGTTTGTGGTCCGGTTTCAGAGAGCTA
CTGCAGAGTAAGAACATGTCCTCATCTCCGCCAGCCGAAACATGGCCACATCAGCTGTTCTACAAGGGAAATGTTA
TATAAGACAACATGTTTGGTTGCCTGTGATGAAGGGTACAGGCTAGAAGGCAGTGATAAGCTTACTTGTCAAGGAA
ACAGCCAGTGGGATGGGCCAGAACCCCGGTGTGTGGAGCGCCACTGTTCCACCTTTCAGATGCCCAAAGATGTCAT
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CAATGTTACCTGGCAGATTCCAACAGCTAAAGACAACCTCTGGTGAAGGTGTGAGTCCACGTTTCATCCAGCTTTC
ACCCACCTTACCTTTTCCAATGGAGATGTTGCTATCGTATACACGGCAACTGACCTATCCGGCAACCAGGCCA
GCTGCATTTTCCATATCAAGGTTATTGATGCAGAACCACTGTATAGACTGGTGCAGATCTCCACCTCCCGTCCA
GGTCTCGGAGAAGGTACATGCCGCAAGCTGGGATGAGCCTCAGTTCTCAGACAACCTCAGGTGCTGAATTGGTCATT
ACCAGAAGTCATACACAAGGAGACCTTTTCCCTCAAGGGGAGACTATAGTACAGTATACAGCCACTGACCCCTCAG
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GGGTCTACTGACAAGTATTATTGTGCTTATGAAGATGGCGTCTGGAAACCAACATATACCACTGAATGGCCAGACT

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AGGCCACCTGTGTGGATGAATTAAATTCATACAGTTGTAAATGTCAAGCAGGATTTTCAGGCAAAAGGTGTGAAAC
AGAACAGTCTACAGGCTTTAACCTGGATTTTGAAGTTTCTGGCATCTATGGATATGTCTAGATGGCATGCTC
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CGTACACAGGAGATGGGAAAACTGTGCAGAACCTATAAAATGTAAGGCTCCAGGAAATCCGGAATGGCCACTC
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ATATACTCTGGCCGGTGATAAAGAATCATCCTGTCTTGCTAACAGTTCTTGGAGTCATTCCCCTCCTGTGTGTGAA
CCAGTGAAGTGTTCTAGTCCGGAATATAAATAATGGAAAATATATTTTGTAGTGGGCTTACCTACCTTTCTACTG
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GCCTGGCCGACGGCAAGTGGAGTAGAAGTGACCAGCAGTGCCCTGGCTGTCTCCTGTGATGAGCCACCCATTGTGGA
CCACGCCTCTCCAGAGACTGCCCATCGGCTCTTTGGAGACATTGCATTCTACTACTGCTCTGATGGTTACAGCCTA
GCAGACAATTTCCAGCTTCTCTGCAATGCCAGGGCAAGTGGGTACCCCAAGAGGTCAGACATGCCCGGTTGTA
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GCTATGCAAGTGGATCAAACCTACAGTTTGGAGCCATGGTGGCTTACAGCTGCAACAAGGGGTTCTACATCAAAGG
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GAACCACCTAAGGTTGAGAATGGCTTTCTGGAGCATACAACCTGGCAGGATCTTTGAGAGTGAAGTGAAGTATCAGT

GTAACCCGGGCTATAAGTCAGTCGGAAGTCCTGTATTGTCTGCCAAGCCAATCGCCACTGGCACAGTGAATCCCC
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GCTAGTATTAAAGGAGTTGACCACCGAGGTAGGAGTTGTGACATTTTCTGTAAAGAAGGGCATGTCCTGCAAGGC
CCCTCTGTCTGAAATGCTTGCCATCCAGCAATGGAATGACTCTTTCCCTGTTTGTAAAGATTGTTCTTTGTACCC
CACCTCCCCTAATTTCTTTGGTGTCCCCATTCTTTCTTCTGCTCTTCATTTTGGAGTACTGTCAAGTATTCTTG
TGAGGTGGGTTTTTCTAAGAGGAAATTTCTACCACCCTCTGCCAACCTGATGGCACCTGGAGCTCTCCACTGCCA
GAATGTGTTCAGTAGAATGTCCCCAACCTGAGGAAATCCCCAATGGAATCATTGATGTGCAAGGCCTTGCCTATC
TCAGCACAGCTCTCTATACCTGCAAGCCAGGCTTTGAATTGGTGGGAAATACTACCACCCTTTGTGGAGAAAATGG
TCACTGGCTTGGAGGAAAACCAACATGTAAAGCCATTGAGTGCCTGAAACCCAAGGAGATTTTGAATGGCAAATTC
TCTTACACGGACCTACACTATGGACAGACCGTTACCTACTCTTGCAACCGAGGCTTTGCGCTCGAAGGTCCCAGTG
CCTTGACCTGTTTAGAGACAGGTGATTGGGATGTAGATGCCCCATCTTGCAATGCCATCCACTGTGATTCCCCACA
ACCCATTGAAAATGGTTTTGTAGAAGGTGCAGATTACAGCTATGGTGCCATAATCATCTACAGTTGCTTCCCTGGG
TTTCAGGTGGCTGGTCATGCCATGCAGACCTGTGAAGAGTCAGGATGGTCAAGTTCCATCCCAACATGTATGCCAA
TAGACTGTGGCCTCCCTCCTCATATAGATTTTGGAGACTGTACTAAACTCAAAGATGACCAGGGATATTTTGGAGCA
AGAAGACGACATGATGGAAGTCCATATGTGACTCCTCACCTCCTTATCATTTGGGAGCAGTGGCTAAAACCTGG
GAAAATACAAAGGATCTCTGTCTACACATTCAAACTTTCTGTATGGTACCATGGTTTTCATACACCTGTAATC
CAGGATATGAACCTTCTGGGGAACCTGTGCTGATCTGCCAGGAAGATGGAACCTTGAATGGCAGTGCACCATCCTG
CATTTCAATTGAATGTGACTTGCCTACTGCTCCTGAAATGGCTTTTGGCGTTTTACAGAGACTAGCATGGGAAGT
GCTGTGCAGTATAGCTGTAAACCTGGACACATTTCTAGCAGGCTCTGACTTAAGGCTTTGTCTAGAGAATAGAAAGT
GGAGTGGTGCCTCCCCACGCTGTGAAGCCATTTCTAGCAAAAAGCCAAATCCAGTCATGAATGGATCCATCAAAGG
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CAGCCAATGGCCAGGTGAGAGGAGACGAGTACACATTCCAAAAAGAGATTGAATACACTTGCATGAAGGTTCTTT
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AGATGTGCCACCCCGCCCAACTGGCCAATGGGGTGACGGAAGGCTGGACTATGGCTTCATGAAGGAAGTAACAT
TCCACTGTACAGAGGGCTACATCTTGACGGTGCTCCAAAACCTCACCTGTCACTCAGATGGCAACTGGGATGCAGA
GATTCCTCTCTGTAAACAGTCAACTGTGGACCTCCTGAAGATCTTGCCCATGGTTTCCCTAATGGTTTTCTCTTT
ATTCTGAGGGGCCATATACAGTATCAGTGCTTTCTGGTTATAAGCTCCATGGAATTCATCAAGAAGGTGCCTCT
CCAATGGCTCCTGGAGTGGCAGCTCACCTTCTGCTGCTTGCAGATGTTCCACACCAGTAATTGAATATGGAAC
TGTCATGGGACAGTATTTGACTGTGGAAGGCGAGCCCGGATTCAAGTCTTCAAAGGCTTCAAGCTCCTAGGACTT
TCTGAAATCACCTGTGAAGCCGATGGCCAGTGGAGCTCTGGGTTCCCCACTGTGAACACACTTCTTGTGGTTCTC
TTCCAATGATACCAATGCGTTTCATCAGTGAGACCACTCTTGAAGGAAAATGTGATAACTTACAGCTGCAGGTC
TGGATATGTCATACAAGGCAGTTTCAGATCTGATTTGTACAGAGAAAGGGTATGGAGCCAGCCTTATCCAGTCTGT
GAGCCCTTGTCTGTGGGTCCCCACCGTCTGTGCGCAATGCACTGGCAACTGGAGAGGCACACACCTATGAAAGTG
AAGTGAAACTCAGATGTCTGGAAGGTTATACGATGGATAACAGATACAGATACATTACCTGTGAGAAAGATGGTCTG
CTGGTTCCCTGAGAGAATCTCTGCAGTCTTAAAAATGTCTCTCCCGGAAAACATAACACATATACTTGTACAT
GGGACGATTTCACTGTGAATAGGCAAGTTTCTGTGTATGTGTCAGAAAGGTATACCTTTGAGGGGATAACATAT
CAGTATGTCTAGCTTGATGGAACCTGGGAGCCACATTCTCCGATGAATCTTGAGTCCAGTTTCTTGTGGGAAACC
TGAAAGTCCAGAACATGGATTTGTGGTTGGCAGTAAATACACCTTTGAAAGCACAAATTATTTATCAGTGTGAGCCT
GGCTATGAACTAGAGGGGAACAGGGAACGTGTCTGCCAGGAGAACAGACAGTGGAGTGGAGGGGTGGCAATATGCA
AAGAGACCAGGTGTGAAACTCCACTTGAATTTCTCAATGGGAAAGCTGACATTGAAAACAGGACGACTGGACCCAA
CGTGGTATATTCTTGCAACAGAGGCTACAGTCTTGAAGGGCCATCTGAGGCACACTGCACAGAAAATGGAACCTGG
AGCCACCCAGTCCCTCTCTGCAACCAAAATCCATGCCCTGTTCTTTTGTGATTCCCGAGAATGCTCTGCTGTCTG
AAAAGGAGTTTTATGTTGATCAGAATGTGTCCATCAAATGTAGGGAAGGTTTTCTGCTGCAGGGCCACGGCATCAT
TACCTGCAACCCCGACGAGACGTGGACACAGACAAGCGCCAAATGTGAAAAATCTCATGTGGTCCACCAGCTCAC
GTAGAAAAATGCAATGCTCGAGGCGTACATTATCAATATGGAGACATGATCACCTACTCATGTTACAGTGGATACA
TGTTGGAGGGTTTTCTGAGGAGTGTGTTTGTAGAAAATGGAACATGGACATCACCTCCTATTTGAGAGCTGTCTG
TCGATTTCCATGTGCAAAATGGGGCATCTGCCAACGCCCAAATGCTTGTCTGTCCAGAGGGCTGGATGGGGCGC
CTCTGTGAAGAACCAATCTGCATTCTTCCCTGTCTGAACGGAGGTGCTGTGTGGCCCTTACCAGTGTGACTGCC
CGCCTGGCTGGACGGGGTCTCGCTGTCTACACGCTGTTTGGCAGTCTCCCTGCTTAAATGGTGGAAAATGTGTAAG
ACCAAACCGATGTCACTGTCTTTCTTCTTGGACGGGACATACTGTTCCAGGAAAAGGAGGACTGGGTTTTAAACCA
CTGCACGACCATCTGGCTCTCCCAAAAGCAGGATCATCTCTCCTCGGTAGTGCCTGGGCATCTGGAACCTTATGCA
AAGAAAGTCCAACATGGTGTGGTCTTGTGTTAGTAAACTTGTACTTGGGGTTACTTTTTTATTTTGTGATATA
TTTTGTTATTCCTGTGACATACTTTCTTACATGTTTCCATTTTTTAAATATGCCTGTATTTTCTATATAAAATTA
TATTAAATAGATGCTGCTCTACCTCACAAAATGTACATATTCTGCTGTCTATTGGGAAAGTTCCTGGTACACATT

TTTATTTCAGTTACTTAAAATGATTTTTCATTAAAGTATATTTTGCTACTAAATAAAAAAA

The sequence of NOV2a was derived by laboratory cloning of cDNA fragments, by *in silico* prediction of the sequence. The cDNA fragments covering either the full length of the DNA sequence, or part of the sequence, or both, were cloned. *In silico* prediction was based on sequences available in CuraGen's proprietary sequence databases or in the public human sequence databases, and provided either the full length DNA sequence, or some portion thereof.

The DNA sequence and protein sequence for a novel polydom-like gene were obtained by SeqCalling™ Technology and are reported here as NOV2a. These methods used to amplify NOV2a cDNA are described in Example 2.

The NOV2a polypeptide (SEQ ID NO:6) encoded by SEQ ID NO:5 is 3570 amino acid residues in length and is presented using the one-letter amino acid code in Table 2B. The SignalP, Psort and/or Hydropathy results predict that NOV2a has a signal peptide and is likely to be localized extracellularly with a certainty of 0.3846. In alternative embodiments, a NOV2a polypeptide is located to the lysosome (lumen) with a certainty of 0.1900, the endoplasmic reticulum (membrane) with a certainty of 0.1000, or the endoplasmic reticulum (lumen) with a certainty of 0.1000. The SignalP predicts a likely cleavage site for a NOV2a peptide between amino acid positions 16 and 17, i.e. at the dash in the sequence VSG-WA.

Table 2B. Encoded NOV2a Protein Sequence (SEQ ID NO:6)

MRRICAACWGLALVSGWATFQQMSPSRNFSFRLFPETAPGAPGSI PAPPAPGDEAAGSRVERLGQAFVRLLR
ELSERLELVFLVDDSSSVGEVNFSELMFVRKLLSDFPVVPTATRVAVITFSSKNYVVPVDYISTRARRQHK
CALLLQEI PAISYRGGGT YTKGA FQQAQ ILLHARENSTKVFLITDGY SNGGDP RP IAASLRDSGVEIFTFG
IWQGNIRELNDMASTPKEEH CYLLHS FEEFEALVALCHMLFVDLP SG SFIQDDMVHCSYL CDEGKDC CDRMGS
CKCGKHTGHFECICEKGYNGKGLQYDCTVCPSGTYKPEGSPGGISSCIPC DENHTSPPGSTSPEDCVCREGY
RASGQTCEVVHCPAL KPPENGYFIQNTCNNHFNAACGV RCHPGFDLVGSSIILCLPNGLWSGSESYCRVRTCP
HLRQPKHGHIS CSTREMLYKTTCLVACDEGYRLEGSDKLT CQGNSQWDGPEPRCVERHCSTFQMPKDVIISPH
NCGKQPAKFGTICYVSCRQGFILSGVKEMLRCTTSGKWNVGVQAAVCKDVEAPQINCPKDIEAKTLEQQDSAN
VTWQIPTAKDNSGEKVS VHVHPAFTPPYLFPIGDVAIVYTATDL SGNQASCIFHIKVIDAEPPVIDWCRSPPP
VQVSEKVHAASWDEPQFSDNSGAELVITRSHTQGD LFPQGETIVQYTATDP SGNNRTCDIHIVIKGSPCEIPF
TPVNGDFICTPDNTGVNCTLTLCLEGYDFTEGSTDKYYCAYEDGVWKPTYTTEWPD CASKRFANHGFKSFEMFY
KAARCDTDLMKKFSEAFETTLGKMVPSFCSDAEDIDCRLEENLT KKYCLEYNYDYENGFAIGPGGWGAANRL
DYSYDDFLDTVQETATSIGNAKSSRIKRSAPLS DYKIKLIFNITASVPLPDERNDTLEWENQORLLQTLETIT
NKLKRTL NKDPMYSFQLASEILIADSN SLETKKASPF CRPGSVLRGRMCVNCPLGTYNLEHFTCESCRIGSY
QDEEGQLECKLCPSGMYTEYIHSRNISDCKAQCKQGTYSYSGLETCE SCPLGTYQPKFGSRSCLS CPENTSTV
KRGAVNISACGVPCPEGKFSRSGLMPCHPCPRDYQPNAGKAFCLACPFYGTTPFAGSR SITECSSFSSTFSA
AEESVVPASLGH IKRHEISSQASHECFNPNCHNSGTCQQLGRGYVCLCPLGYTGLKCETDIDECSP LCLN

NGVCKDLVGEFICECPSGYTGHCELNINECQSNPCRNQATCVDELNSYSCKCQPGFSGKRCETGMYQLSVIN
 NLNNAVCEDQVGGFLCKCPPGFLGTRCGKNVDECLSQPCKNGATCKDGANSFRCLCAAGFTGSHCELNINECQ
 SNPCRNQATCVDELNSYSCKCQPGFSGKRCETEQTSTGFNLD FEVSGIYGYVMDGMLPSLHALTCTFWMKSSD
 DMNYGTPISYAVDNGSDNTLLLTIDYNGWVLYVNGREKITNCPSVNDGRWHHIAITWTSTGGAWRVYINGELSD
 GGTGLSIGKAIPGGGALVLGQEQDKKGEFNPAPESFVGSISQLNLWDYVLSPPQVKSLATSCPEELSKGNVLA
 WPDFLSGIVGKVKIDSKSIFCSDCPRLGGSVPHLRTASEDLKPGSKVNLFCBPGLVGNPVQYCLNQGWQTQ
 PLPHCERIRCGVPPPLENGFHSADDFYAGSTVTYQCNNGYLLGDSRMFCTDNGSWNGVSPSCLDVECAVGS
 DCSEHASCLNVDSYICSCVPPYTGDGKNCAEPIKCKAPGNPENGHSSGEIYTVGAEVTFSCQEGYQLMGVTK
 ITCLESGEWNHLIPYCKAVSCGKPAIPENGCIIELAFTFGSKVTYRCNKGYTLAGDKESSCLANSSWSHSPPV
 CEPVKCSSPENINNGKYILSGLTYLSTASYSCTDGYSLQGPSIIECTASGIWDRAPPACHLVFCGEPPAIKDA
 VITGNNFTFRNTVTYTYCKEGYTLAGLDTIECLADGKWSRSDQOCLAVSCDEPPIVDHASPETAHRLFGDIAFY
 YCSDGYSLADNSQLLCAOQKWVPEPQDMPRCIAHFCEKPPSVSYSILESVSKAKFAAGSVVSVFKCMEGFVL
 NTSKIECMRGGQWNPSPMSIQCIIPVRCGEPPSIMNGYASGNSYSGAMVAYSCKNGFYIKGEKKSTCEATGQ
 WSSPIPTCHPVSCGEPPKVENGFLHTTGRIFESEVRYQCNPGYKSVGSPVFCQANRHHWSESPLMCVPLDC
 GKPPPIQNGFMKGNEFEVGSKVQFFCNEGYELVDSSWTCQKSGKWNKSNPKCMPAKCPEPPLLENQLVLKE
 LTTEVGVVTFSCKEGHVLQGPSVLKCLPSQQWNSDFPVCKIVLCTPPPLISFGVPIPSALHFGSTVKYSCVG
 GFFLRGNSTLTCQPDGTWSSPLPECVPVECPQPEEIPNGIIDVQGLAYLSTALYTCCKPGFELVGNNTTLTCLGEN
 GHWLGGKPTCKAIECLKPKEILNGKFSYTDLHYGQTVTYSCNRGFRLEGPSALTCTLETGDWDVDAPSCNAIHC
 DSPQPIENGFEVGEADYSYGAI IYSCFPGFQVAGHAMQTCEESGWSSSIPTCMPIDCGLPPHIDFGDCTKLKD
 DQGYFEQEDDMEVPYVTPHPYHLGAVAKTWENTKESPATHSSNPLYGTMVSYTCNPGYELLGNPVLICQED
 GTWNGSAPSCISIECDLPTAPENGFLRFTETSMGSAVQYSCPKGHILAGSDLRLCLENRKWSGASPRCEAISC
 KKPMPVMNGSIKGSNYTYLSTLYEYCDPGYVLNGTERTCQDDKNWDEDEPICIPVDCSSPPVSANGQVRGDE
 YTFQKEIYTCNEGFLLEGARSVCLANGSWGATPDCVPVRCATPPQLANGVTEGLDYGFMEKVTTFHCHEGY
 ILHGAPKLTCQSDGNWDAEIPLCKPVNCGPPEDLAHGFPNGFSFIHGGHIQYQCFPGYKLHGNSSRRCLNNGS
 WSGSSPSCLPSCRSTPVIIEYGTVNGTDFDCGKAARIQCFCGKFLGLSEITCEADGQWSSGFPHCEHTSCGSL
 PMIPNAFISSETSSWKENVITYISCRSGYVIQSSDLICTEKGWVSQPYVCEPLSCGSPPSVANAVATGEAHTY
 ESEVKLRCLLEGYTMDDTDFTFCQKDGWRWFERISCSPPKCPLENITHILVHGDDFSVNRQVSVSCAEGYTF
 EGVNISVCQLDGTWEPPFSDSCSPVSCGKPESEHGFFVVGSKYTFESTIIYQCEPGYELEGNRRVCQENRQ
 WSGGVAICKETRCETPLEFLNGKADIENRTTGNVYVSCNRGYSLEGPSEAHCTENGTSWHPVPLCKPNPCPV
 PFVIPENALLSEKEFYVDQNVSIKCREGFLQGHGIITCNPDDETWTQTSACEKISCGPPAHVENAARGVHY
 QYGDMITYSCYSGYMLGFLRSVCLENGTTWSPPI CRAVCRFPQNGGICQRPNACSCPEGWMGRCLCEEPICI
 LPLCLNGGRCVAPYQCDCPPGWTGSRCHTAVCQSPCLNGGKCVRPNRCHCLSSWTGHNCSRKRRTGF

NOV2b

In an alternative embodiment, a NOV2 variant is NOV2b (alternatively referred to herein
 as CG50646-05), which includes the 11152 nucleotide sequence (SEQ ID NO:7) shown in Table
 2C. An open reading frame for the mature protein was identified beginning with an ATG codon
 at nucleotides 77-79 and ending with a termination codon at nucleotides 10781-10783. The start
 and stop codons of the open reading frame are highlighted in bold type. Putative untranslated
 regions are underlined and found upstream from the initiation codon and downstream from the
 termination codon.

Table 2C. NOV2b Nucleotide Sequence (SEQ ID NO:7)

CAATTGGTCTAGGGTCTCCCCATTGGAATATCCATCAGTGATGAGAAATACAACGTTTGTGAGTTTTC
 TCTAGCATGAGAAGAATTTGCGCGGCTTGCTGGGGTCTGGCGCTCGTTTCGGGCTGGGCGACCTTTCAGC
 AGATGTCCCGTCGCGCAATTTTCAGCTTCCGCCTCTTCCCCGAGACCGCGCCCGGGGCCCCGGGAGTAT
 CCCCCGCGCCCGCTCCTGGCGACGAAGCGGCGGGGAGCAGAGTGAGCGGCTGGGCCAGGCGTTCCGC
 GTGCGGCTGCTGCGGGAGCTCAGCGAGCGCCTGGAGCTTGTCTTCTGGTGGATGATTCGTCCAGCGTGG
 GCGAAGTCAACTTCCGCGAGCGAGCTCATGTTCTGTCGCAAGCTGCTGTCCGACTTCCCCGTGGTGCCAC
 GGCCACGCGCGTGGCCATCGTGACCTTCTCGTCCAAGAACTACGTGGTGCCGCGCGTTCGATTACATCTCC
 ACCCGCCGCGCGCGCCAGCACAAGTGCGCGCTGCTCCTCCAAGAGATCCCTGCCATCTCTACCGAGGTG
 GCGGCACCTACACCAAGGGCGCCTTCCAGCAAGCCGCGCAAATTTCTTTCATGCTAGAGAAAACCTCAAC
 AAAAGTTGTATTTCTCATCACTGATGGATATTCCAATGGGGGAGACCCTAGACCAATTGCAGCGTCACTG
 CGAGATTGAGGAGTGAGATCTTCACTTTTGGCATATGGCAAGGGAACATTTCGAGAGCTGAATGACATGG
 CTTCCACCCCAAGGAGGAGCACTGTTACCTGCTACACAGTTTTGAAGAATTTGAGGCTTTAGCTCGCCG
 GGCATTGCATGAAGATCTACCTTCTGGGAGTTTTATTCAAGATGATATGGTCCACTGCTCATATCTTTGT
 GATGAGGGCAAGGACTGCTGTGACCGAATGGGAAGCTGCAAATGTGGGACACACACAGGCCATTTTGTAGT
 GCATCTGTGAAAAGGGGTATTACGGGAAAGGTCTGCAGTATGAATGCACAGCTTGCCCATCGGGACATA
 CAAACCTGAAGCCTCACCAGGAGGAATCAGCAGTTGCATTCCATGTCCCGATGAAAATCACACCTCTCCA
 CCTGGAAGCACATCCCCGTAAGACTGTGTCTGCAGAGAGGGATACAGGGCATCTGGCCAGACCTGTGAAC
 TTGTCCACTGCCCTGCCCTGAAGCCTCCCGAAAATGGTTACTTTATCCAAAACACTTGCAACAACCACTT
 CAATGCAGCCTGTGGGGTCCGATGTCAACCTGGATTGTATCTTGTGGGAAGCAGCATCATCTTATGTCTA
 CCCAATGGTTTGTGGTCCGGTTCAGAGAGCTACTGCAGAGTAAGAACATGTCTCATCTCCGCCAGCCGA
 AACATGGCCACATCAGCTGTTCTACAAGGGAAATGTTATATAAGACAACATGTTTGGTTGCCCTGTGATGA
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 AACCAGGCCAGCTGCATTTTCCATATCAAGGTTATTGATGCAGAACCACCTGTATAGACTGGTGCAGAT
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 GTACAGTATACAGCCACTGACCCCTCAGGTAATAACAGGATATGTGATATCCATATTGTATGAAAGGTT
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 GCTTCAAGCTCCTAGGACTTTCTGAAATCACCTGTGAAGCCGATGGCCAGTGGAGCTCTGGGTTCCTCCA
 CTGTGAACACACTTCTGTGGTTCTCTCCAATGATACCAATGCGTTTCATCAGTGAGACCAGCTCTTTGG
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 CGCCAATGCAGTGGCAACTGGAGAGGCACACACCTATGAAAGTGAAGTGAACCTCAGATGTCTGGAAGGT
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 GGACGACTGGACCCAACGTGGTATATTCCTGCAACAGAGGCTACAGTCTTGAAGGGCCATCTGAGGCACA
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 GTGATTCCCAGAAATGCTCTGCTGTCTGAAAAGGAGTTTTATGTTGATCAGAATGTGTCCATCAAATGTA
 GGAAGGTTTTCTGCTGCAGGGCCACGGCATCATTACCTGCAACCCCGACGAGACGTGGACACAGACAAG
 CGCCAATGTGAAAAAATCTCATGTGGTCCACAGCTCACGTAGAAAAATGCAATTGCTCGAGGCGTACAT
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 TTTGTTTAGAAAAATGGAACATGGACATCACCTCCTATTTGCAGAGCTGTCTGTCGATTTCATGTGAGAA
 TGGGGGCATCTGCCAACGCCCAAATGCTTGTCTGTCAGAGGGCTGGATGGGGCGCTCTGTGTAAGAA
 CCAATCTGCATTCTTCCCTGTCTGAACGGAGGTCTGCTGTGTGGCCCTTACCAGTGTGACTGCCCGCCTG
 GCTGGACGGGTCTCGCTGTGATACAGCTGTTTGCCAGTCTCCCTGCTTAAATGGTGGAAAAATGTGTAAG
 ACCAAACCGATGTCACTGTCTTTCTTCTGACGGGACATAACTGTTCCAGGAAAAGGAGGACTGGGTTT
 TAACCACTGCACGACCATCTGGCTCTCCCAAAGCAGGATCATCTCTCCTCGGTAGTGCCTGGGCATCCT
 GGAACCTATGCAAGAAAGTCCAACATGGTGTGGGTCTTGTGTTAGTAACTGTGTTACTTGGGGTTACTT
 TTTTATTTTGTGATATATTTGTTATTCCTGTGACATACTTTCTTACATGTTTCCATTTTAAATATG
 CCTGTATTTCTATATAAAAAATTATATTAAATAGATGCTGCTCTACCTCACAAAATGTACATATCTGCT
 TGTCTATTGGGAAAGTTCTGGTACACATTTTTATTAGTTACTTAAATGATTTTTCCATTAAAGTATA
 TTTTGCTACTAAATAAAAAAAA

The sequence of NOV2b was derived by laboratory cloning of cDNA fragments, by *in silico* prediction of the sequence. The cDNA fragments covering either the full length of the DNA

sequence, or part of the sequence, or both, were cloned. *In silico* prediction was based on sequences available in CuraGen's proprietary sequence databases or in the public human sequence databases, and provided either the full length DNA sequence, or some portion thereof.

The DNA sequence and protein sequence for a novel polydom-like gene were obtained by SeqCalling™ Technology and are reported here as NOV2b. These methods used to amplify NOV2b cDNA are described in the Example 2.

The NOV2b polypeptide (SEQ ID NO:8) encoded by SEQ ID NO:7 is 3568 amino acid residues in length and is presented using the one-letter amino acid code in Table 2D. The SignalP, Psort and/or Hydropathy results predict that NOV2b has a signal peptide and is likely to be localized extracellularly with a certainty of 0.3846. In alternative embodiments, a NOV2b polypeptide is located to the lysosome (lumen) with a certainty of 0.1900, the endoplasmic reticulum (membrane) with a certainty of 0.1000, or the endoplasmic reticulum (lumen) with a certainty of 0.1000. The SignalP predicts a likely cleavage site for a NOV2b peptide between amino acid positions 16 and 17, i.e. at the dash in the sequence VSG-WA.

Table 2D. Encoded NOV2b Protein Sequence (SEQ ID NO:8)

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MRRICAAWGLALVSGWATFQQMSPSRNFSFRLFPETAPGAPGSIPAPPAPGDEAAGSRVERLGQAFVRLLRELS
ERLELVFLVDDSSSVGEVNFSELMFVRKLLSDFPVVPATRAIVTFSSKNYVVPVVDYISTRRARQHKCALLLQ
EIPAISYRGGGTYTKGAQQAAQILLHARENSTKVFLITDGYSNGGDRPIAASLRDSGVEIPTFGIWQGNIREL
NDMASTPKEEHCYLLHSFEEFEALARRALHEDLPSGSFIQDDMVHCSYLCDEGKDCDRMGSCCKGTHTGHECIC
EKGYGKGLQYECTACPSGTYPKPEASPGGISSCIPCPDENHTSPPGSTSPEDCVCREGYRASQTCELVHCPALKP
PENGFIQNTCNNHFNAACGVRCHPGFDLVGSSIILCLPNGLWSGESYCRVRTCPHLRQPKHGHISCSSTREMLYK
TTCLVACDEGYRLEGSCLKTCQNSQWDGPEPRCVERHCSTFQMPKDVIIISPHNCGKQPAKFGTICYVSCRQGFIL
SGVKEMLRCTTSGKWNVGVQAAVCKDVEAPQINCPKDIEAKTLEQQDSANVTWQIPTAKDNSGEKVSVRVHPAFTP
PYLFPIGDVAIVYTATDLSGNQASCIFHIKVIDAEPVIDWCRSPPPVQVSEKVHAASWDEPQFSDNSGAELVITR
SHTQGDLPQGETIVQYTATDPSGNNRICDIHIVMKGSPCEIPFTPVNGDFICTPDNTGVNCTLTCLLEGYDFTEGS
TDKYYCAYEDGVWKPTYTTEWPDCAKKRFANHGFKSFEMFYKAARCDSDLMKKFSEAFETTLGKMVPSFCSDAED
IDCRLEENLTKKYCLEYNYDYENGFAIGPGWGGAANRLDYSYDDFLDTVQETATSIGNAKSSRIKRSAPLSDYKIK
LIFNITASVPLPDERNDTLEWENQORLLQTLETITNKLRKTLNKDPMYSFQLASEILADSNSLETKKASPFRCRPG
SVLRGRMCVNCPLGTYYNLEHFTCESCRIGSYQDEEGQLECKLCPSGMYTEYIHSRNISDCKAQCKQGTYSYSGLE
TCESCPLGTYQPKFGSRSCSCPENTSTVKRGAVNISACGVPCPEGKFSRSGLMPCHPCPRDYYPNAGKAFCLAC
PFYGTTPFAGRSITECSSFSSTFSAAEESVPPASLGHIKKRHEISSQASHECFNPNCHNSGTCCQLGRGYVCLC
PLGYTGLKCETDIDECSPPLCLNNGVCKDLVGEFICECPSGYTGKHCNELNINECQSNPCRNQATCVDELNSYSCKC
QPGFSGKRCETGMYQLSVINNLNNAVCEDQVGGLCKCPGFLGTRCGKNVDECLSQPCKNQATCKDGANSFRCLC
AAGFTGSHCELNINECQSNPCRNQATCVDELNSYSCKCQPGFSGKRCETEQTGFNLD FEVSGIYGYVMDGMLPS
LHALTCTFWMKSSDDMNYGTPISYAVDNGSDNTLLLT DYNGWVLYVNGREKITNCPSVNDGRWHIAITWTSTGGA
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LSKGNVLAWPDLFSGIVGVKIDSKSIFCSDCPRLGGSVPHLRTASEDLKPGSKVNLFCEPGFQLVGNPVQYCLNQ
GQWTQPLPHCERIRCGVPPPLENGFHSADDFYAGSTVTYQCNNGYLLGDSRMFCTDNGSWNGVSPSCLDVDECAV
GSDCSEHASCLNVDGSYICSCVPPYTGDGKNCAEPIKCKAPGNPENGHSSGEIYTVGAEVTFSCQEGYQLMGVTKI
TCLESGEWNHLIPYCKAVSCGKPAIPENGCIELAFTFGSKVTYRCNKGYTLAGDKESSCLANSSWSHSPVCEPV
KCSSPENINNGKYILSGLTYLSTASYSCTDGYSLQGPSIIECTASGIWDRAPPACHLVFCGEPPAIKDAVITGNNF
TFRNTVTYTCKEGYTLAGLDTIECLADGKWSRSDQQLAVSCDEPPIVDHASPETAHRLFGLDIAFYCSDGYSLAD

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NSQLLCNAQGWVPPEGQDMPCIAHFCEKPPSVSYSILESVS KAKFAAGSVVSFKCMEGFVLNTSAKIECMRGGQ
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 PKVENGFLEHTTGRI FESEVRYQCNPGYKSVGSPVFCQANRHHWSESPLMCVPLDCGKPPPIQNGFMKGNEFEVG
 SKVQFFCNEGYELVGDSSWTCQKSGKWNKSNPKCMPAKCEPPLLENQLVLKELTTEVGVVTFSCKEGHVLOGPS
 VLKCLPSQQWNSFPVCKIVLCTPPPLISFGVPI PSSALHFGSTVKYSCVGGFFLRGNSTTLCQPDGTWSSPLPEC
 VPVECPQPEEIPNGIIDVQGLAYLSTALYTCKPGFELVGN'TTTL CGENGHWLGGKPTCKAIECLKPKEILNGKFSY
 TDLHYGQTVTYSCNRGFRLEGPSALTCLETGDWDVDAPSCNAIHCDSPQPIENG FVEGADYSYGAI I IYSCFPGFQ
 VAGHAMQTCEESGWSSSIPTCMPIDCGLPPHIDFGDCTKLKDDQGYFEQEDDMMEVPYVTPHPYHLGAVAKTWEN
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 QDDKNWDEDEPI CIPVDCSSPPVSANGQVRGDEYTFQKEIEYTCNEGFLLEGARSRVCLANGSWSGATPDCVPVRC
 ATPPQLANGVTEGLDYGFMKEVTFHCHEGYILHGAPKLTCSQSDGNWDAE I PLCKPVNCGPPEDLAHGFPNGFSFIH
 GGHIQYQCFFPGYKLHGNSRRCLSNWSGSSPSCLP CRCSTPVIEYGTVNGTDFDCGKAARIQCFKGFKLLGLSE
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 LSCGSPPSVANAVATGEAHTYSEVKLRCLGYTMDTDTFTCQKDG RWFPERISCS PKKCPLENITHILVHGD
 DFSVNRQVSVC AEGYTFEGVNISVCQLDGTWEPPFSDESCSPVSCGKPESPEHGFVVGSKYTFESTIIYQCEPG
 ELEGNRERVCQENRQWSGGVAICKETRCETPLEFLNGKAD IENRTTGPNNVYSCNRGYSLEGPS EAHCTENGTTWSH
 PVPLCKPNPCPVFPVIPENALLSEKEFYVDQNVSIKCREGFLLOGHGII TCNPDETWTQTS AKCEKISC GPPAHVE
 NAIARGVHYQYGD MITYSCYSGYMLEGFLRSVCLNGTWTSPPICRAVCRFP CQNGGICQRPNACSCPEGWMGRLC
 EEPICILPCLNGGRCVAPYQCD CPPGWTGSRCHTAVCQSPCLNGGKCVRPNRCHCLSSWTGHNC SRKRRTGF

SNP variants of NOV2 are disclosed in Example 3.

NOV2 Clones

Unless specifically addressed as NOV2a or NOV2b, any reference to NOV2 is assumed to encompass all variants.

The amino acid sequence of NOV2 has high homolgy to other proteins as shown in Table 2E.

Table 2E. BLASTX Results from Patp Database for NOV2

		High	Smallest
Sequences Producing High-Scoring Segment Pairs:		Score	Sum Prob P (N)
patp:AAM93954	Human polypeptide,	8375	0.0
patp:AAB94754	Human protein sequence	7012	0.0
patp:AAU16963	Human novel secreted protein	6452	0.0
patp:AAU18126	Novel human uterine motility-association po...	6452	0.0
patp:AAG66398	Receptor 222 - Unidentified	5577	0.0

In a search of sequence databases, it was found, for example, that the NOV2a nucleic acid sequence has 2414 of 2422 bases (99%) identical to a gb:GENBANK-

ID:HST000009|acc:AL079279.1 mRNA from Homo sapiens (Homo sapiens mRNA full length insert cDNA clone EUROIMAGE 248114). Further, the full amino acid sequence of the

disclosed NOV2a protein of the invention has 2895 of 3567 amino acid residues (81%) identical

to, and 3181 of 3567 amino acid residues (89%) similar to, the 3567 amino acid residue ptrn:TREMBLNEW-ACC:AAG32160 protein from *Mus musculus* (Mouse) (POLYDOM PROTEIN PRECURSOR).

In a similar search of sequence databases, it was found, for example, that the NOV2b nucleic acid sequence has 7556 of 9127 bases (82%) identical to a gb:GENBANK-ID:AF206329|acc:AF206329.1 mRNA from *Mus musculus* (*Mus musculus* polydom protein mRNA, complete cds). Further, the full amino acid sequence of the disclosed NOV2b protein of the invention has 2902 of 3565 amino acid residues (81%) identical to, and 3189 of 3565 amino acid residues (89%) similar to, the 3567 amino acid residue ptrn:SPTREMBL-ACC:Q9ES77 protein from *Mus musculus* (Mouse) (POLYDOM PROTEIN PRECURSOR).

Additional BLASTP results are shown in Table 2F.

Table 2F. NOV2 BLASTP Results					
Gene Index/ Identifier	Protein/Organism	Length of aa	Identity (%)	Positives (%)	Expect Value
Q9ES77	POLYDOM PROTEIN PRECURSOR - <i>Mus musculus</i> (Mouse)	3567	289/3567 (81%)	3181/3567 (89%)	0.0
BAB55420	CDNA FLJ14964 FIS, CLONE PLACE4000581, MODERATELY SIMILAR TO FIBROPELLIN I PRECURSOR - <i>Homo sapiens</i> (Human)	1316	1255/1316 (95%)	1267/1316 (96%)	0.0
AAH08135	POLYDOMAIN PROTEIN - <i>Mus musculus</i> (Mouse)	669	534/668 (79%)	594/668 (88%)	0.0
Q9CUT3	4833413O10RIK PROTEIN - <i>Mus musculus</i> (Mouse)	601	483/601 (80%)	538/601 (89%)	2.4e-298
Q9H284	SEROLOGICALLY DEFINED BREAST CANCER ANTIGEN NY- BR-38 - <i>Homo sapiens</i> (Human)	481	458/482 (95%)	462/482 (95%)	1.8e-261

A multiple sequence alignment is given in Table 2G, with the NOV2 protein of the invention being shown in lines 1 and 2, in a ClustalW analysis comparing NOV2 with related protein sequences of Table 2F.

Table 2G. ClustalW Analysis of NOV2

5	1. SEQ ID NO.: 6	NOV2a	5. SEQ ID NO.: 49	AAH08135
	2. SEQ ID NO.: 8	NOV2b	6. SEQ ID NO.: 50	Q9CUT3
	3. SEQ ID NO.: 47	Q9ES77	7. SEQ ID NO.: 51	Q9H284
	4. SEQ ID NO.: 48	BAB55420		
10	NOV2a	-----	1	
	NOV2b	-----	1	
	Q9ES77	MWSRLAFCCWALALVSGWTNFQPVAPSLNFSFRLFPEASPGALGRLAVPPASSEEEAAGS	60	
	BAB55420	-----	1	
	AAH08135	-----	1	
15	Q9CUT3	-----	1	
	Q9H284	-----	1	
20	NOV2a	-----	1	
	NOV2b	-----	1	
	Q9ES77	KVERLGRAFRSRVRLRELSGSLELVFLVDESSSVGQTNFLNELKFVRKLLSDFPVVSTA	120	
	BAB55420	-----	1	
	AAH08135	-----	1	
	Q9CUT3	-----	1	
25	Q9H284	-----	1	
	NOV2a	-----	1	
	NOV2b	-----	1	
	Q9ES77	TRVAIVTFSSKNNVVARVDYISTSRHQHKCALLSREIPAITYRGGGTYTKGAFQQAQI	180	
30	BAB55420	-----	1	
	AAH08135	-----	1	
	Q9CUT3	-----	1	
	Q9H284	-----	1	
35	NOV2a	-----	1	
	NOV2b	-----	1	
	Q9ES77	LRHSRENSTKVIFLITDGYSNGGDRPIAASLRDFGVEIFTFGIWQGNIRELNDMASTPK	240	
	BAB55420	-----	1	
	AAH08135	-----	1	
40	Q9CUT3	-----	1	
	Q9H284	-----	1	
45	NOV2a	-----	1	
	NOV2b	-----	1	
	Q9ES77	EEHCYLLHSFEEFEALARRALHEDLPSGSFIQEDMARCSYLCEAGKDCCDRMASCKCGTH	300	
	BAB55420	-----	1	
	AAH08135	-----	1	
	Q9CUT3	-----	1	
50	Q9H284	-----	1	
	NOV2a	-----	1	
	NOV2b	-----	1	
	Q9ES77	TGQFECICEKGYYGKGLQHECTACPSGTYKPEASPGGISTCIPCPDVSHTSPPGSTSPED	360	
55	BAB55420	-----	1	
	AAH08135	-----	1	
	Q9CUT3	-----	1	
	Q9H284	-----	1	

	NOV2a	-----	
	NOV2b	-----	1
	Q9ES77	CVCREGYQSRSGQTCEVVHCPALKPPENGFFIQNTCKNHFNAAACGVRCRPGFDLVGSS IHL	420
5	BAB55420	-----	1
	AAH08135	-----	1
	Q9CUT3	-----	1
	Q9H284	-----	1
		-----	1
10	NOV2a	-----	1
	NOV2b	-----	1
	Q9ES77	CQPNGLWSGTESFCRVTCPHLRQPKHGHISCSTAEMSYNTLCCLVTCNEGVRLEGSTRLT	480
	BAB55420	-----	1
	AAH08135	-----	1
15	Q9CUT3	-----	1
	Q9H284	-----	1
		-----	1
	NOV2a	-----	1
	NOV2b	-----	1
20	Q9ES77	CQGNQWDGPEPRCVERHCATFQKPKGVIIISPPSCGKQPARPGMTCQLSCRQGYILSGVR	540
	BAB55420	-----	1
	AAH08135	-----	1
	Q9CUT3	-----	1
	Q9H284	-----	1
25		-----	1
	NOV2a	-----	1
	NOV2b	-----	1
	Q9ES77	EVRCATSGKWSAKVQTAVCKDVEAPQISCPNDIEAKTGEQQDSANVTWQVPTAKDNSGEK	600
30	BAB55420	-----	1
	AAH08135	-----	1
	Q9CUT3	-----	1
	Q9H284	-----	1
		-----	1
35	NOV2a	-----MRRICAACWGLALVSGWATFQQMSPSRNFSFRLFP	35
	NOV2b	-----	1
	Q9ES77	VSVHVHPAFTPPYLPPIGDVAITYTATDSSGNQASCTFYIKVIDVEPPVIDWCRSPPIQ	660
	BAB55420	-----	1
	AAH08135	-----	1
	Q9CUT3	-----	1
40	Q9H284	-----	1
		-----	1
	NOV2a	ETAPGAPGSIPAPPAPGDEAAGSRVERLGQAFRVRLRLRELSELELVFLVDDSSSVGEVN	95
	NOV2b	-----	1
45	Q9ES77	VVEKEHPASWDEPQFSDNSGAELVITSSHTQGDMFPHGETVVWYTATDPGNNRTCDIHI	720
	BAB55420	-----	1
	AAH08135	-----	1
	Q9CUT3	-----	1
	Q9H284	-----	1
		-----	1
50	NOV2a	FRSELMFVRKLLSDFPVVPTATRVVAIVTFSSKNYVVPVDYISTRARRQHKCALLLQEIIP	155
	NOV2b	-----	1
	Q9ES77	VIKGSPCEVPFTPVNGDFICAQDSAGVNCSLSCKEGYDFTEGSTEKYYCAFEDGIWRPPY	780
	BAB55420	-----	1
	AAH08135	-----	1
55	Q9CUT3	-----	1
	Q9H284	-----	1
		-----	1

	NOV2a	AISYRGGGTYTKGAFQQAQILLHARENSTKVFLITDGYSNGGDPRPIAASLRDSGVEI	215
	NOV2b	-----	1
	Q9ES77	STEWPDCAIKRFANHGFKSFEMLYKTTTRCDDMDLFFKKFSAAFETTLGNMVPSFCNDADDI	840
5	BAB55420	-----	1
	AAH08135	-----	1
	Q9CUT3	-----	1
	Q9H284	-----	1
10	NOV2a	FTFGIWQGNIRELNDMASTPKEEH CYLLHSFEEFEALVALCHMLFVDLP SG SFIQDDMVH	275
	NOV2b	-----	1
	Q9ES77	DCRLEDLTKKYCIEYNYN YENGFAIGPGGWGAGNRLDYSYDHFLDVVQETPTDVGKARSS	900
	BAB55420	-----	1
	AAH08135	-----	1
	Q9CUT3	-----	1
15	Q9H284	-----	1
	NOV2a	CSYLCDEGKDCCDRMGSCCKGKHTGHFECICEKGYNGKGLQYDCTVCPSGTYKPEGSPGG	335
	NOV2b	-----	1
	Q9ES77	RIKRTVPLSDPKIQLIFNITASVPLPEERNDTLELENQQRLIKLTLETITNRLKSTLNKEP	960
20	BAB55420	-----	1
	AAH08135	-----	1
	Q9CUT3	-----	1
	Q9H284	-----	1
25	NOV2a	ISSCIPCPDENHTSPPGSTSPEDCVCREGYRASGQTCEVVHCPALKPPENGYFIQNTCNN	395
	NOV2b	-----	1
	Q9ES77	MYSFQLASETVVADSNSLETEKAFLFCRPGSVLRGRMCVNCPLGTSYSLEHSTCESCLMG	1020
	BAB55420	-----	1
	AAH08135	-----	1
30	Q9CUT3	-----	1
	Q9H284	-----	1
	NOV2a	HFNAACGVRCHPGFDLVGSSIIILCLPNGLWSGSES YCRVRTCPHLRQPKHGHISCSTREM	455
	NOV2b	-----	1
35	Q9ES77	SYQDEEGQLECKLCPPTHTEYLHSRSVSECKAQCKQGTYS SSGLETCE SCPLGTYQPEF	1080
	BAB55420	-----	1
	AAH08135	-----	1
	Q9CUT3	-----	1
	Q9H284	-----	1
40	NOV2a	LYKTTCLVACDEGYRLEGSDKLT CQGNSQWDGPEPRCVERHCSTFQMPKDVII SPHNC GK	515
	NOV2b	-----	1
	Q9ES77	GSRSCLLCPETTTT VKRGAVDISACGVPCPVGEFSRSGLT PCYPCPRDYQPNAGKSFCL	1140
	BAB55420	-----	1
45	AAH08135	-----	1
	Q9CUT3	-----	1
	Q9H284	-----	1
50	NOV2a	QPAKFGTICYVSCRQGFILSGVKEMLRCTTSGKWNVGVQAAVCKDVEAPQINCPKDIEAK	575
	NOV2b	-----	1
	Q9ES77	ACPFYGT TTTITGATSITDCSSFSSTFSAAEESIVPLVAPGHSQNKYEVS S QVFHECFLNP	1200
	BAB55420	-----	1
	AAH08135	-----	1
	Q9CUT3	-----	1
55	Q9H284	-----	1
	NOV2a	TLEQQDSANVTWQIPTAKDNSGEKVS VHVHPAFTPPYLPPIGDVAIVYTATDL SGNQASC	635

	NOV2b	-----	
	Q9ES77	CHNSGTCQQLGRGYVCLCPPGYTGLKCETDIDECSSLPCLNGGICRDQVGGFTCECSLGY	1
	BAB55420	-----	1260
	AAH08135	-----	1
5	Q9CUT3	-----	1
	Q9H284	-----	1
		-----	1
	NOV2a	IFHIKVIDAEPPVIDWCRSPPPVQVSEKVHAASWDEPQFSDNSGAELVITRSHTQGDLP	695
	NOV2b	-----	
10	Q9ES77	SGQICEENINECTISSPCLNKGTCTDGLASYRCTCVKGYMGVHCETDVNECQSSPCLNNAV	1
	BAB55420	-----	1320
	AAH08135	-----	1
	Q9CUT3	-----	1
	Q9H284	-----	1
15		-----	1
	NOV2a	QGETIVQYTATDPGSGNNRTCDIHIVIKGSPCEIPFTPVNGDFICTPDNTGVNCTLTCL	755
	NOV2b	-----	
	Q9ES77	CKDQVGGFSCCKCPPGFLGTRCEKNVDECLSQPCQNGATCKDGANSFRCQCPAGFTGTHCE	1
	BAB55420	-----	1380
20	AAH08135	-----	1
	Q9CUT3	-----	1
	Q9H284	-----	1
		-----	1
	NOV2a	YDFTEGSTDKYYCAYEDGVWKPTYTTEWPCASKRFANHGFKSFEMFYKAARCDTDLMK	815
25	NOV2b	-----	
	Q9ES77	LNINECQSNPCRNQATCVDELNSYSCKCQPGFSGHRCETEQPSGFNLDFEVSGIYGYVLL	1
	BAB55420	-----	1440
	AAH08135	-----	1
	Q9CUT3	-----	1
30	Q9H284	-----	1
		-----	1
	NOV2a	KFSEAFETTLGKMVPSFCSDAEDIDCRLEENLTKKYCLEYNYDYENGFAIGPGGWAANR	875
	NOV2b	-----	
	Q9ES77	DGVLPTLHAITCAFWMKSSDVINYGTPISYALEDDKDNTSLLTDYNGWVLYVNGKEKITN	1
35	BAB55420	-----	1500
	AAH08135	-----	1
	Q9CUT3	-----	1
	Q9H284	-----	1
		-----	1
	NOV2a	LDYSYDDFLDTVQETATSIGNAKSSRIKRSAPLSDYKIKLIFNITASVPLPDERNDTLEW	935
40	NOV2b	-----	
	Q9ES77	CPSVNDGIWHHIAITWTSTGGAWRVYINGELSDGGTGLSIGKAIPGGGALVLGQEQDKKG	1
	BAB55420	-----	1560
	AAH08135	-----	1
45	Q9CUT3	-----	1
	Q9H284	-----	1
		-----	1
	NOV2a	ENQORLLQTLETITNKLKRTLKNDPMYSFQLASEILIADSNLSLETKKASPFRCRPGSVLRG	995
	NOV2b	-----	
50	Q9ES77	EGFNPAESFVGSISQLNLWDYVLSPOQVKLLASSCPEELSRGNVLAWPDFLSGITGKVKV	1
	BAB55420	-----	1620
	AAH08135	-----	1
	Q9CUT3	-----	1
	Q9H284	-----	1
55		-----	1
	NOV2a	RMCVNCPLGTYYNLEHFTCESCRIGSYQDEEGQLECKLCPSGMYTEYIHSRNISDCKAQC	1055
	NOV2b	-----	
		-----	1

5	Q9ES77	DSSSMFCSDCPSLEGSVPHLRPASGNRKP GSKVSLFCDPGFQMVGNPVQYCLNQGWTPQ	1680
	BAB55420	-----	1
	AAH08135	-----	1
	Q9CUT3	-----	1
	Q9H284	-----	1
10	NOV2a	KQGTYSYSGLETCESCLGTYQPKFGSRSC LSCPENTSTVKRGAVNISACGVPCPEGKFS	1115
	NOV2b	-----	1
	Q9ES77	LPHCERIRCGLPPALENGFYSAEDFHAGSTVTYQCTSGYYLLGDSRMFCTDNGSWNGISP	1740
	BAB55420	-----	1
	AAH08135	-----	1
	Q9CUT3	-----	1
20	Q9H284	-----	1
	NOV2a	RSGLMPCHPCPRDYYQPNAGKAFCLACPFYGTTPFAGSRSITECSSFSSTFSAAEESVVP	1175
	NOV2b	-----	1
	Q9ES77	SCLDVDECAVGSDCSEHASCLNTNGSYVCSCNPPYTGDGKNCAEPVKCKAPENPENGHSS	1800
	BAB55420	-----	1
	AAH08135	-----	1
30	Q9CUT3	-----	1
	Q9H284	-----	1
	NOV2a	PASLGHIKKRHEISSQASHECFNPNCHNSGTCQQLGRGYVCLCPLGYTGLKCETDIDECS	1235
	NOV2b	-----	1
	Q9ES77	GEIYTVGTAVTFSCDEGHELVGVSTITCLETGEWDRLRPSCEAISC GVPPVPENGVDGS	1860
	BAB55420	-----	1
35	AAH08135	-----	1
	Q9CUT3	-----	1
	Q9H284	-----	1
	NOV2a	PLPCLNNGVCKDLVGEFICECPSGYTGKHCELNINECQSNPCRNQATCVDELNSYSCKCQ	1295
	NOV2b	-----	1
	Q9ES77	AFTYGSKVVYRCDKGYTLSGDEESACLASGSWSHSSPVCELVKCSQPEDINNGKYILSGL	1920
40	BAB55420	-----	1
	AAH08135	-----	1
	Q9CUT3	-----	1
	Q9H284	-----	1
	NOV2a	PGFSGKRCETGMYQLSVINN LNNAVCEQVGGFLCKCPPGFLGTRCGKNVDECLSQPCKN	1355
	NOV2b	-----	1
45	Q9ES77	TYLSIASYSCENGYSIQGPSLLECTAGS WDRAPPSQLVSCGEPPIVKDAVITGSNFTF	1980
	BAB55420	-----	1
	AAH08135	-----	1
	Q9CUT3	-----	1
	Q9H284	-----	1
	NOV2a	GATCKDGANSFRCLCAAGFTGSHCELNINECQSNPCRNQATCVDELNSYSCKCQPGFSGK	1415
50	NOV2b	-----	1
	Q9ES77	GNTVAYTCKEGYTLAGPDTIVCQANGKWNSSNHQCLAVSCDEPPNVDHASPETAHRLFGD	2040
	BAB55420	-----	1
	AAH08135	-----	1
	Q9CUT3	-----	1
	Q9H284	-----	1
55	NOV2a	RCETEQSTGFNLDFEVSGIYGVM LDGMLPSLHALTCTFWMKSSDDMNYGTPISYAVDNG	1475
	NOV2b	-----	1
	Q9ES77	TAFYYCADGYSLADNSQLICNAQGNWVPPAGQAVPRCIAHFCEKPPSVSYSILES VSKAK	2100

	BAB55420	-----	1
	AAH08135	-----	1
	Q9CUT3	-----	1
	Q9H284	-----	1
5		-----	1
	NOV2a	SDNTLLLLTDYNGWVLYVNGREKITNCPSVNDGRWEHIAITWTSTGGAWRVYINGELSDGG	1535
	NOV2b	-----	1
	Q9ES77	FAAGSVVSFKCMEGFVLNTSAKIECLRGGEWSPSPLSVQCIPVRCGEPPSIANGYPSTGN	2160
10	BAB55420	-----	1
	AAH08135	-----	1
	Q9CUT3	-----	1
	Q9H284	-----	1
		-----	1
15	NOV2a	TGLSIGKAIPGGGALVLGQEQDKKGEFNPAES.FVGSISQLNLWDYVLSPQQVKSLATSC	1595
	NOV2b	-----	1
	Q9ES77	YSFGAVVAYSCHKGFYIKGEKKSTCEATGQWSKPTPTCHPVSCNEPPKVENGFLHETTGR	2220
	BAB55420	-----	1
	AAH08135	-----	1
	Q9CUT3	-----	1
20	Q9H284	-----	1
		-----	1
	NOV2a	PEELSKGNVLAWPDFLSGIVGKVKIDSKSIFCSDCPRLGGSVPHLRTASEDLKPGSKVNL	1655
	NOV2b	-----	1
25	Q9ES77	TFESEARFQCNPGYKAAGSPVFVCQANRHWHS DAPLSCTPLNCGKPPPIQNGFLKGESFE	2280
	BAB55420	-----	1
	AAH08135	-----	1
	Q9CUT3	-----	1
	Q9H284	-----	1
		-----	1
30	NOV2a	FCEPGFQLVGNPNVOYCLNQGQWTQPLPHCERIRCGVPPPLENGFHSADDFYAGSTVTYQC	1715
	NOV2b	-----	1
	Q9ES77	VGSKVQFVCNEGYELVGDNSTWCQKSGKWSKKPSPKCVPTKCAEPPLLENQLVLKELASE	2340
	BAB55420	-----	1
35	AAH08135	-----	1
	Q9CUT3	-----	1
	Q9H284	-----	1
		-----	1
	NOV2a	NNGYYLLGDSRMFCTDNGSWNGVSPSCLDVDECAVGSDCSEHASCLNVDGSYICSCVPPY	1775
40	NOV2b	-----	1
	Q9ES77	VGVMTISCKEGHALQGPSVLKCLPSGQWNGSFPICKMVLCPSPPLIPFGVPASSGALHFG	2400
	BAB55420	-----	1
	AAH08135	-----	1
	Q9CUT3	-----	1
45	Q9H284	-----	1
		-----	1
	NOV2a	TGDGKNCAEPIKCKAPGNPENGHSSGEIYTVGAEVTFSCQEGYQLMGVTKITCLESGEWN	1835
	NOV2b	-----	1
	Q9ES77	STVKYLCVDGFFLRGSPTILCQADSTWSSPLPECVPVECPQPEEILNGIIHVQGLAYLST	2460
50	BAB55420	-----	1
	AAH08135	-----	1
	Q9CUT3	-----	1
	Q9H284	-----	1
		-----	1
55	NOV2a	HLIPYCKAVSCGKPAIPENGCIIELAFTFGSKVTYRCNKGYTLAGDKESSCLANSSWSHS	1895
	NOV2b	-----	1
	Q9ES77	TLYTCKPGFELVGNATTLCGENGQWLGGKPMCKPIECPEPKEILNGQFSSVSFQYGQTIT	2520
	BAB55420	-----	1

	AAH08135	-----	1
	Q9CUT3	-----	1
	Q9H284	-----	1
5	NOV2a	PPVCEPVKCSSPENINNGKYILSGLTYLSTASYSCDTGYSLQGPSIIIECTASGIWDRAPP	1955
	NOV2b	-----	1
	Q9ES77	YFCDRGFRLEGPKSLTCLTGDWDMDPPSCDAIHCSDPQPIENG FVEGADYRYGAMIIYS	2580
	BAB55420	-----	1
	AAH08135	-----	1
10	Q9CUT3	-----	1
	Q9H284	-----	1
	NOV2a	ACHLVFCGEPPAIPKDAVITGNFTFRNTVTYTCKEGYTLAGLDTIECLADGKWSRSDQQC	2015
	NOV2b	-----	1
15	Q9ES77	CFPGFQVLGHAMQTCEESGWSSSSPTCVPIDCGLPPHIDFGDCTKVRDGGHFDQEDDM	2640
	BAB55420	-----	1
	AAH08135	-----	1
	Q9CUT3	-----	1
	Q9H284	-----	1
20	NOV2a	LAVSCDEPPIVDHASPETAHRLFGDIAFYYSYSDGYSLADNSQLLCNAQGWVPPEGQDMP	2075
	NOV2b	-----MRRICACWGLALVSGWATFQQMSPSRNFSFR	32
	Q9ES77	EVPLYLAHPQHLEATAKALENTKES PASHASHFLYGTMVSYSCPEPGYELLGIPVLICQEDG	2700
	BAB55420	-----	1
25	AAH08135	-----	1
	Q9CUT3	-----	1
	Q9H284	-----	1
	NOV2a	RCIAHFCEKPPSVSYSILESVS KAKFAAGSVVSFKCMEGFVLNTSAKIECMRGGQWNPSP	2135
30	NOV2b	LFPETAPGAPGSIPAPPAPGDEAAGSRVERLGOAFRVRLRLSERLELVFLVDDSSSVG	92
	Q9ES77	TWNGTAPSCISIECDLPVAPENGFLHFTQTTMGSAAQYSCKPGHILEGSHLRLCLQNKQW	2760
	BAB55420	-----	1
	AAH08135	-----	1
	Q9CUT3	-----	1
35	Q9H284	-----	1
	NOV2a	MSIQICIPVRCEPPSIMNGYASGSNYSFGAMVAYSCNKGFIYKGEKKSTCEATGQWSSPI	2195
	NOV2b	EVNFRSELMFVRKLLSDFPVPTATRVAVITFSSKNYVVPVDYISTRRARQHKCALLLQ	152
	Q9ES77	SGTVPRCEAISCSPNPLWNGSIKDDYSYLGVLVYECDSGYILNGSKKRTCQENRDWDG	2820
40	BAB55420	-----	1
	AAH08135	-----	1
	Q9CUT3	-----	1
	Q9H284	-----	1
45	NOV2a	PTCHPVSCGEPPKVENGFLHTTGRIFESEVRYQCNP GYKSVGSPVFCQANRHWHSERP	2255
	NOV2b	EIPAI SYRGGGTYTKGA FQQAQIILLHARENSTKVFLITDGY SNGGDPRIAASLRDSG	212
	Q9ES77	HEPMCIPVDCGSPVPPTNGRVKGEEYTFQKEITYSCREGFILEGARSRICLTNGSWSGAT	2880
	BAB55420	-----	1
	AAH08135	-----	1
50	Q9CUT3	-----	1
	Q9H284	-----	1
	NOV2a	LMCVPLDCGKPPPIQNGFMKG ENFEVGSKV OFFCNEGYELVGDSSWTCQKSKWNKKS NP	2315
	NOV2b	VEIFTFGIWQGNIRELNDMASTPKEEH CYLLHSFEEFEALARRALHEDLPSCSFIQDDMV	272
55	Q9ES77	PSCMPVRC PAPPQVPNGVADGLDYGFKKEVAFHCLEGYVLOQAPRLTCQSNGTWD-AEVP	2939
	BAB55420	-----MASTPKEEH CYLLHSFEEFEALARRALHEDLPSCSFIQDDMV	42
	AAH08135	-----ADGLDYGFKKEVAFHCLEGYVLOQAPRLTCQSNGTWD-AEVP	41

	Q9CUT3	-----	1
	Q9H284	-----MKGENFEVGSKVQFFCNEGYELVGDSSWTCQKSKWANKKSNP-----	42
5	NOV2a	KOMPAKCPPEPPLLENQLVLKELTTEVGVMTFSCKEGHVLOG-----PS-----	2358
	NOV2b	HCS-YLCDEGKDCDRMGSCCKGTHTGHEFCICEKGYGKGLQYECTACPSGTYKPEASP	331
	Q9ES77	VCKPATCGPPADLPQGFPNGFSFYHGHHIQYOCFTGYKHLHG-----NPS-----	2983
	BAB55420	HCS-YLCDEGKDCDRMGSCCKGTHTGHEFCICEKGYGKGLQYECTACPSGTYKPEGSP	101
	AAH08135	VCKPATCGPPADLPQGFPNGFSFYHGHHIQYOCFTGYKHLHG-----NPS-----	85
10	Q9CUT3	-----HIQYOCFTGYKHLHG-----NPS-----	17
	Q9H284	KOMPAKCPPEPPLLENQLVLKELTTEVGVMTFSCKEGHVLOG-----PS-----	85
15	NOV2a	--VLKCLPSQQWNSFP-----VCKIVLCTPPPLISFGVPPIP-SS	2395
	NOV2b	GGISSCIPCPDENHTSPPGSTSPEDCVCREGYRASGQTCELVHCPALKPPENGYFIQNTC	391
	Q9ES77	---RRCLPNGSWSGSSP-----SCLPCRCSTPIIQOG--TIN-AT	3017
	BAB55420	GGISSCIPCPDENHTSPPGSTSPEDCVCREGYRASGQTCELVHCPALKPPENGYFIQNTC	161
	AAH08135	---RRCLPNGSWSGSSP-----SCLPCRCSTPIIQOG--TIN-AT	119
	Q9CUT3	---RRCLPNGSWSGSSP-----SCLPCRCSTPIIQOG--TIN-AT	51
	Q9H284	--VLKCLPSQQWNSFP-----VCKIVLCTPPPLISFGVPPIP-SS	122
20	NOV2a	ALHFGSTVKYSCVGGFFLRGNSTTLCQPDGTWSSPLPECVPVECPQPEEIPNGHIDVQG-	2454
	NOV2b	NNHFNAACGVRRCHPGFDLVGSSIIILCLPNGLWSGESYCRVRTCPHLRQPKHGHTSCSTR	451
	Q9ES77	DLGCCKTIVQIECFKGFKLGLSEITCDANGOWSD-VPLCEHAOCGPLPTIPNATVLEGS-	3075
	BAB55420	NNHFNAACGVRRCHPGFDLVGSSIIILCLPNGLWSGLESYCRVRTCPHLRQPKHGHTSCSTR	221
	AAH08135	DLGCCKTIVQIECFKGFKLGLSEITCDANGOWSD-VPLCEHAOCGPLPTIPNATVLEGS-	177
25	Q9CUT3	DLGCCKTIVQIECFKGFKLGLSEITCDANGOWSD-VPLCEHAOCGPLPTIPNATVLEGS-	109
	Q9H284	ALHFGSTVKYSCVGGFFLRGNSTTLCQPDGTWSSPLPECVPVECPQPEEIPNGHIDVQG-	181
30	NOV2a	-LAYLSTALYTCKPGFELVGNITTLCEGNGHWLGGKPTCKATEC---LKPKEILNG--KF	2508
	NOV2b	EMLYKTTCLVACDEGYRLEGSCKLTCQGNSSQWDPPEPRCVERHCSTFQMPKDVIIISPHNC	511
	Q9ES77	-LSEDNVVTYSCRPGYTMQSSDLICTEKAIWSQPYPTCEPLSCG---PPPTVANA--VA	3129
	BAB55420	EMLYKTTCLVACDEGYRLEGSCKLTCQGNSSQWDPPEPRCVERHCSTFQMPKDVIIISPHNC	281
	AAH08135	-LSEDNVVTYSCRPGYTMQSSDLICTEKAIWSQPYPTCEPLSCG---PPPTVANA--VA	231
	Q9CUT3	-LSEDNVVTYSCRPGYTMQSSDLICTEKAIWSQPYPTCEPLSCG---PPPTVANA--VA	163
35	Q9H284	-LAYLSTALYTCKPGFELVGNITTLCEGNGHWLGGKPTCKATEC---LKPKEILNG--KF	235
40	NOV2a	SYTDLHYGQTVTYSCNRGRLEGP-SALTCLETCDWDVDAPSCNAIHCDSPQP-----TE	2562
	NOV2b	GKQPAKEGTICYVSCRQGFILSGVKEMLRCTTSGKNNVGVQAAVCKDVEAPQINCPKDIE	571
	Q9ES77	TGEAHTYESKVKLRCLLEGYVMSDSDTDTFTCQDGHVPERITCSPKKCPVPSN-----MT	3184
	BAB55420	GKQPAKEGTICYVSCRQGFILSGVKEMLRCTTSGKNNVGVQAAVCKDVEAPQINCPKDIE	341
	AAH08135	TGEAHTYESKVKLRCLLEGYVMSDSDTDTFTCQDGHVPERITCSPKKCPVPSN-----MT	286
	Q9CUT3	TGEAHTYESKVKLRCLLEGYVMSDSDTDTFTCQDGHVPERITCSPKKCPVPSN-----MT	218
	Q9H284	SYTDLHYGQTVTYSCNRGRLEGP-SALTCLETCDWDVDAPSCNAIHCDSPQP-----TE	289
45	NOV2a	NGFVEGADYS-----YGAILIYSCFPGEFQ-----VAGHAMQCEESGWSS	2602
	NOV2b	AKTLEQODSANVTWQIPTAKDNSGEKVSVRVHPAFTPPYLFPIGDVAIVYTATDLSGNQA	631
	Q9ES77	RIRFHGDDFQ-----VNROVSVSCAEGFT-----HEGVNWSCTCPDGTWE	3224
	BAB55420	AKTLEQODSANVTWQIPTAKDNSGEKVSVRVHPAFTPPYLFPIGDVAIVYTATDLSGNQA	401
	AAH08135	RIRFHGDDFQ-----VNROVSVSCAEGFT-----HEGVNWSCTCPDGTWE	326
	Q9CUT3	RIRFHGDDFQ-----VNROVSVSCAEGFT-----HEGVNWSCTCPDGTWE	258
50	Q9H284	NGFVEGADYS-----YGAILIYSCFPGEFQ-----VAGHAMQCEESGWSS	329
55	NOV2a	---SIPTCMPIDCGLPHPHIDFGDCTKIKDDQGYFEQEDDMMEVPYVTPH-----PPYH	2652
	NOV2b	---SCIFHLKVIDAEPVIDWCRSPPPVQVSEKVAAS-WDEPQFSDNSGAELVITRSH	687
	Q9ES77	PPFSDDESCIPVVCCHPESPAHGSVVGNNHSGSTIVYQCDPGYKLEGNR-ERICQENRQW	3283
	BAB55420	---SCIFHLKVIDAEPVIDWCRSPPPVQVSEKVAAS-WDEPQFSDNSGAELVITRSH	457
	AAH08135	PPFSDDESCIPVVCCHPESPAHGSVVGNNHSGSTIVYQCDPGYKLEGNR-ERICQENRQW	385
	Q9CUT3	PPFSDDESCIPVVCCHPESPAHGSVVGNNHSGSTIVYQCDPGYKLEGNR-ERICQENRQW	317

Q9H284	---SIPTCMPIIDCGLEPHIDFGACTKLKDARDILSKKR-HDGSSICDSS-----PSLS	378
NOV2a	LGAVAKTWENTKESPATHSS-----NFLY-----GTMVS	2681
NOV2b	QGDIFPQGETIVQYTATDPSGNNRICDIHIVMKGSPCEIPFTPVNGDFICTPDNTGVNCT	747
Q9ES77	SGEVAVCRENRCETPAEFPNG-----KAVLENTTSGPSLL	3318
BAB55420	QGDIFPQGETIVQYTATDPSGNNRTCDIHIVIKGSPCEIPFTPVNGDFICTPDNTGVNCT	517
AAH08135	SGEVAVCRENRCETPAEFPNG-----KAVLENTTSGPSLL	420
Q9CUT3	SGEVAVCRENRCETPAEFPNG-----KAVLENTTSGPSLL	352
Q9H284	FGAVAKTWENTKESPATHSS-----NFLY-----GTMVS	407
NOV2a	YTCNPGYELLG---NPVLIQOEDGTWN-----	2705
NOV2b	LTCLEGYDFTEGSTDKYYCAYEDGVWKPTYTTEWPDCAKKRFANHGFKSFEMFYKAARCD	807
Q9ES77	FSCHRGYTLEG---SPEAHCTANGTWN-----	3342
BAB55420	LTCLEGYDFTEGSTDKYYCAYEDGVWKPTYTTEWPDCAKKRFANHGFKSFEMFYKAARCD	577
AAH08135	FSCHRGYTLEG---SPEAHCTANGTWN-----	444
Q9CUT3	FSCHRGYTLEG---SPEAHCTANGTWN-----	376
Q9H284	YTCNPGYELLG---NPVLIQOEDGTWN-----	431
NOV2a	-----GSAPSCIS---IECDLETAP-----ENGFLR---	2728
NOV2b	DSDLMKKFSEAFETTLGKMVPSFCSDAEDIDCRLEENLTCKYCLEYNYDYENGFAIGPGG	867
Q9ES77	-----HLTPLCKP---NPCPVPFVIP-----ENAVLS---	3366
BAB55420	DTDLMKKFSEAFETTLGKMVPSFCSDAEDIDWRLEENLTCKYCLEYNYDYENGFAIGPGG	637
AAH08135	-----HLTPLCKP---NPCPVPFVIP-----ENAVLS---	468
Q9CUT3	-----HLTPLCKP---NPCPVPFVIP-----ENAVLS---	400
Q9H284	-----GSAPSCIS---IECDLETAP-----ENGFLR---	454
NOV2a	-----FTETSMGSAVOYSCKPGHILAGSDLRCLCLENRKWSGASPRC	2769
NOV2b	WGAANRLDYSYDDFLDTVQETATSIGNAKSSRIKRSAPISDYKIKLIFNITASVPLPDER	927
Q9ES77	-----EKEFYVDQNVSIKCREGFLKNGVITCS-----P----	3396
BAB55420	WGAANRLDYSYDDFLDTVQETATSIGNAKSSRIKRSAPISDYKIKLIFNITASVPLPDER	697
AAH08135	-----EKEFYVDQNVSIKCREGFLKNGVITCS-----P----	498
Q9CUT3	-----EKEFYVDQNVSIKCREGFLKNGVITCS-----P----	430
Q9H284	-----FTETSMGSAVOYSCKPGHILAGSDLRCLCLENRKWSGASPRC	481
NOV2a	EAISCKKPNPVMNGSIKGSNYTYLSTLYEEDPGYVLNGTERRTCQDDKNWDEDEPICIP	2829
NOV2b	NDTLEWENQORLLQTLTITITNKLKRTLKDPMSYFQLASEILIADSNLSLETKKASPF CRP	987
Q9ES77	-----DE-----	3398
BAB55420	NDTLEWENQORLLQTLTITITNKLKRTLKDPMSYFQLASEILIADSNLSLETKKASPF CRP	757
AAH08135	-----DE-----	500
Q9CUT3	-----DE-----	432
Q9H284	-----DE-----	481
NOV2a	VDCSSPPVVSANGQVRGDEYTFQKEIEYTCNEGFLLEGARSRVCLANGSWGATPDCVPVR	2889
NOV2b	GSVLRGRMCVNCPLGTYYNLEHFTCESCRIGSYQDEEGQLECKLCPSGMYTEYIHSRNIS	1047
Q9ES77	-----TWHTNARCEKISCGP-----PSHVE	3419
BAB55420	GSVLRGRMCVNCPLGTYYNLEHFTCESCRIGSYQDEEGQLECKLCPSGMYTEYIHSRNIS	817
AAH08135	-----TWHTNARCEKISCGP-----PSHVE	521
Q9CUT3	-----TWHTNARCEKISCGP-----PSHVE	453
Q9H284	-----TWHTNARCEKISCGP-----PSHVE	481
NOV2a	CATPPQLANGVTEGLDYGFMKEVTFHCHEGYILHGAPKLTCQSDGNWDABEIPLCKPVNCG	2949
NOV2b	DCKAQCKQGTYSSGLETCECPLGTYQPKFGSRSCLSCPENTSTVKRGAVNISACGVPC	1107
Q9ES77	NAIAR-----	3424
BAB55420	DCKAQCKQGTYSSGLETCECPLGTYQPKFGSRSCLSCPENTSTVKRGAVNISACGVPC	877
AAH08135	NAIAR-----	526
Q9CUT3	NAIAR-----	458
Q9H284	NAIAR-----	481

5	NOV2a	PPEDLAHGFPNGFSFIHGGHIQYQCFPGYKIHGNSRRCLSNGSWSGSSPSCLPCRCSTP	3009
	NOV2b	PEGKFSRSGLMPCHPCPRDIYQPNAGKAFCLACPFYGTTPFAGSRSITECSSFSSTFSAA	1167
	Q9ES77	--GVYYQYQCDMITYSCYSGYMLEGSLRSVCLENGWTWTPSP-----	3462
	BAB55420	PEGKFSRSGLMPCHPCPRDIYQPNAGKAFCLACPFYGTTPFAGSRSITECSSFSSTFSAA	937
	AAH08135	--GVYYQYQCDMITYSCYSGYMLEGSLRSVCLENGWTWTPSP-----	564
10	Q9CUT3	--GVYYQYQCDMITYSCYSGYMLEGSLRSVCLENGWTWTPSP-----	496
	Q9H284	-----	481
15	NOV2a	VIEYGTVNGTDFDCGKAARIQCFKGFKLLGLSEITCEADGQWSSGFPHCZHTSCGSLPMI	3069
	NOV2b	EESVVPASLGHIAKKRHEISSQASHECFNPNCHNSGTCQQLGRGYVCLCPLGYTGLKCET	1227
	Q9ES77	-----VCRAVCRFPQNGGVCQ---RPNACSCPDGWMGRLCEE	3497
	BAB55420	EESVVPASLGHIAKKRHEISSQVFHECFNPNCHNSGTCQQLGRGYVCLCPLGYTGLKCET	997
	AAH08135	-----VCRAVCRFPQNGGVCQ---RPNACSCPDGWMGRLCEE	599
20	Q9CUT3	-----VCRAVCRFPQNGGVCQ---RPNACSCPDGWMGRLCEE	531
	Q9H284	-----	481
25	NOV2a	PNAFISETSSWKENVITYSCRSYVIOGSSDLICTEKGWVSQPYPVCEPLSCGSPPSVAN	3129
	NOV2b	DIDECSPCLNNGVCKDLVGEFICECPSGYTGKHCENINECQSNPCRNQATCVDELNS	1287
	Q9ES77	P---ICILPCLNGGRC---VAPYQDCDPTGWTGSRCHTAT---CQSPCLNGGKCIR---P	3545
	BAB55420	DIDECSPCLNNGVCKDLVGEFICECPSGYTGKHCENINECSSSPCLNKGICVDGVAG	1057
	AAH08135	P---ICILPCLNGGRC---VAPYQDCDPTGWTGSRCHTAT---CQSPCLNGGKCIR---P	647
30	Q9CUT3	P---ICILPCLNGGRC---VAPYQDCDPTGWTGSRCHTAT---CQSPCLNGGKCIR---P	579
	Q9H284	-----	481
35	NOV2a	AVATGEAHTYSEVKLRLCLEGYTMDTDTDTFTCQKDGWRWFERISCSPKKCPLPENITHI	3189
	NOV2b	YSCKCQPGFSGKRCETGMYQLSVINLNNVACEDQVGGFLCKCPPGFLGTRCGKNVDECL	1347
	Q9ES77	NRCHCLSAWTGHDCSRKRAGL-----	3567
	BAB55420	YRCTCVKGFVGLHCETEVEVNECQSNPCLNNAVCEQVGGFLCKCPPGFLGTRCGKNVDECL	1117
	AAH08135	NRCHCLSAWTGHDCSRKRAGL-----	669
40	Q9CUT3	NRCHCLSAWTGHDCSRKRAGL-----	601
	Q9H284	-----	481
45	NOV2a	LVHGDDFSVNRQVSVSACAGYTFEGVNISVCQLDGTWEPPFSDESCSPVSCGKPESPEHG	3249
	NOV2b	SQPCKNGATCKDGANSFRCLCAAGFTGSHCELNINECQSNPCRNQATCVDELNSYSCKCQ	1407
	Q9ES77	-----	3567
	BAB55420	SQPCKNGATCKDGANSFRCLCAAGFTGSHCELNINECQSNPCRNQATCVDELNSYSCKCQ	1177
	AAH08135	-----	669
50	Q9CUT3	-----	601
	Q9H284	-----	481
55	NOV2a	FVVGSKYTFESTIIYQCEPGYELEGNRERVCOENRQWSGGVAICKETRCETPLEFLNGKA	3309
	NOV2b	PGFSGKRCETEQTSTGFNLDFFVSGIYGYVMLDGMPLSLHALTCTFWMKSSDDMNYGTPIS	1467
	Q9ES77	-----	3567
	BAB55420	PGFSGKRCETEQTSTGFNLDFFVSGIYGYVMLVGMLPSLHALTCTFWMKSSDDMNYGTPIS	1237
	AAH08135	-----	669
55	Q9CUT3	-----	601
	Q9H284	-----	481
50	NOV2a	DIENRTTGPNVVSVCNRYSGLEGPSEAHCTENGTSWHPVPLCKPNPCPVFPVIPENALLS	3369
	NOV2b	YAVDNGSDNTLLLTIDYNGWVLYVNGREKITNCPSVNDGRWHHIAITWTSTGGAWRVYING	1527
	Q9ES77	-----	3567
	BAB55420	YAVDNGSDNTLLLTIDYNGWVLYVNGREKITNCPSVNDGRWHHIAITWTSANGIWKVYIDG	1297
	AAH08135	-----	669
55	Q9CUT3	-----	601
	Q9H284	-----	481

	NOV2a	EKEFYVDQNVSIKCREGFLLQGHGIITCNPDETWTQTSKCEKISCGPPAHVENAIARGV	3429
	NOV2b	ELSDGGTGLSIGKAIPGGGALVLGQEQDKKGEFNPAESFVGSISQLNLWDYVLSPQQVK	1587
	Q9ES77	-----	3567
5	BAB55420	KLSDGGAGLSVGLPIPG-----MF-----	1316
	AAH08135	-----	669
	Q9CUT3	-----	601
	Q9H284	-----	481
10	NOV2a	HYQYGDMITYSCYSGYMLEGFLRSVCLNGTWTSPPICRAVCRFPQNGGICQRPNACSC	3489
	NOV2b	SLATSCPEELSKGNVLAWPDFLSGIVGKVKIDSKSIFCSDCPRLGGSVPHLRTASEDLKP	1647
	Q9ES77	-----	3567
	BAB55420	-----	1316
	AAH08135	-----	669
	Q9CUT3	-----	601
15	Q9H284	-----	481
	NOV2a	PEGWMGRLCCEPICILPCLNGGRCVAPYQCDCPPGWTGSRCHTAVCQSPCLNGGKCVRPN	3549
	NOV2b	GSKVNLFCPEPGFQLVGNPVQYCLNQGWQTQPLPHCERIRCGVPPPLENGFHSADDFYAGS	1707
	Q9ES77	-----	3567
20	BAB55420	-----	1316
	AAH08135	-----	669
	Q9CUT3	-----	601
	Q9H284	-----	481
25	NOV2a	RCHCLSSWTGHNCSRKRRTGF-----	3570
	NOV2b	TVTYQCNNGYLLGDSRMFCTDNGSWNGVSPSCLDVDECAVGSDCSEHASCLNVDGSYIC	1767
	Q9ES77	-----	3567
	BAB55420	-----	1316
	AAH08135	-----	669
30	Q9CUT3	-----	601
	Q9H284	-----	481
	NOV2a	-----	3570
35	NOV2b	SCVPPYTGDGKNCAEPIKCKAPGNPENGHSSGEIYTVGAEVTFSCQEGYQLMGVTKITCL	1827
	Q9ES77	-----	3567
	BAB55420	-----	1316
	AAH08135	-----	669
	Q9CUT3	-----	601
40	Q9H284	-----	481
	NOV2a	-----	3570
	NOV2b	ESGEWNHLIPYCKAVSCGKPAIPENGCIIELAFTFGSKVITYRCNKGYTLAGDKESSCLAN	1887
	Q9ES77	-----	3567
45	BAB55420	-----	1316
	AAH08135	-----	669
	Q9CUT3	-----	601
	Q9H284	-----	481
50	NOV2a	-----	3570
	NOV2b	SSWSHSPPVCEPVKCSSPENINNGKYILSGLTYLSTASYSCTDGYSLQGPSIIECTASGI	1947
	Q9ES77	-----	3567
	BAB55420	-----	1316
	AAH08135	-----	669
55	Q9CUT3	-----	601
	Q9H284	-----	481
	NOV2a	-----	3570

5	NOV2b	WDRAPPACHLVFCGEPPAIKDAVITGNNFTFRNTVTYTCKEGYTLAGLDTIECLADGKWS	2007
	Q9ES77	-----	3567
	BAB55420	-----	1316
	AAH08135	-----	669
	Q9CUT3	-----	601
10	Q9H284	-----	481
	NOV2a	-----	3570
	NOV2b	RSDQQCLAVSCDEPPIVDHASPETAHRLFGDIAFYCYSDGYSLADNSQLLCNAQGKWWPP	2067
	Q9ES77	-----	3567
	BAB55420	-----	1316
15	AAH08135	-----	669
	Q9CUT3	-----	601
	Q9H284	-----	481
	NOV2a	-----	3570
	NOV2b	EGQDMPRCIAHFCEKPPSVSYSILESVS KAKFAAGSVVSFKCMEGFVLNTSAKIECMRGG	2127
20	Q9ES77	-----	3567
	BAB55420	-----	1316
	AAH08135	-----	669
	Q9CUT3	-----	601
	Q9H284	-----	481
25	NOV2a	-----	3570
	NOV2b	QWNPSPMSIQICIPVRCGEPPSIMNGYASGSNYSFGAMVAYSCNKGFIYKGEKKSTCEATG	2187
	Q9ES77	-----	3567
	BAB55420	-----	1316
	AAH08135	-----	669
30	Q9CUT3	-----	601
	Q9H284	-----	481
	NOV2a	-----	3570
	NOV2b	QWSSPIPTCHPVSCGEPPKVENGFLEHTTGRI FESEVRYQCNP GYKSVGSPVFVCQANRH	2247
	Q9ES77	-----	3567
35	BAB55420	-----	1316
	AAH08135	-----	669
	Q9CUT3	-----	601
	Q9H284	-----	481
	NOV2a	-----	3570
40	NOV2b	WHSESPLMCVPLDCGKPPPIQNGFMKGENFEVGSKVQFFCNEGYELVGDSSWTCQKSGKW	2307
	Q9ES77	-----	3567
	BAB55420	-----	1316
	AAH08135	-----	669
	Q9CUT3	-----	601
45	Q9H284	-----	481
	NOV2a	-----	3570
	NOV2b	NKKS NPKCMPAKCPEPPLLENQLVLKELTTEVG VVTFSCKEGHVLQGPSVLKCLPSQQWN	2367
	Q9ES77	-----	3567
	BAB55420	-----	1316
50	AAH08135	-----	669
	Q9CUT3	-----	601
	Q9H284	-----	481
	NOV2a	-----	3570
	NOV2b	DSFPVCKIVLCTPPPLISFGVPIPSSALHFGSTVKYSCVGGFFLRGNSTTLCQPDGTWSS	2427

	Q9ES77	-----	3567
	BAB55420	-----	1316
	AAH08135	-----	669
	Q9CUT3	-----	601
5	Q9H284	-----	481
	NOV2a	-----	3570
	NOV2b	PLPECVPVECPQPEEIPNGIIDVQGLAYLSTALYTCKPGFELVGNTTTLGGENGHWLGK	2487
10	Q9ES77	-----	3567
	BAB55420	-----	1316
	AAH08135	-----	669
	Q9CUT3	-----	601
	Q9H284	-----	481
15	NOV2a	-----	3570
	NOV2b	PTCKAIECLKPKEILNGKFSYTDLHYGQTVTYSCNRGFRLEGPSALTCLETGDWDVDAPS	2547
	Q9ES77	-----	3567
	BAB55420	-----	1316
	AAH08135	-----	669
20	Q9CUT3	-----	601
	Q9H284	-----	481
	NOV2a	-----	3570
25	NOV2b	CNAIHCDSPQPIENGFEVADYSYGAIIIYSCFPGFQVAGHAMQTCEESGWSSSIPTCMP	2607
	Q9ES77	-----	3567
	BAB55420	-----	1316
	AAH08135	-----	669
	Q9CUT3	-----	601
30	Q9H284	-----	481
	NOV2a	-----	3570
	NOV2b	IDCGLPPHIDFGDCTKLKDDQGYFEQEDDMMEVPYVTPHPPYHLGAVAKTWENTKESPAT	2667
	Q9ES77	-----	3567
	BAB55420	-----	1316
35	AAH08135	-----	669
	Q9CUT3	-----	601
	Q9H284	-----	481
	NOV2a	-----	3570
40	NOV2b	HSSNFLYGTVMVSYTCNPGYELLGNPVLICQEDGTWNGSAPSCISIECDLPTAPENGFLRF	2727
	Q9ES77	-----	3567
	BAB55420	-----	1316
	AAH08135	-----	669
45	Q9CUT3	-----	601
	Q9H284	-----	481
	NOV2a	-----	3570
	NOV2b	TETSMGSAVQYSCKPGHILAGSDLRLCLENRKWGSASPRCEAISCKKPNPVMNGSIKGSN	2787
50	Q9ES77	-----	3567
	BAB55420	-----	1316
	AAH08135	-----	669
	Q9CUT3	-----	601
	Q9H284	-----	481
55	NOV2a	-----	3570
	NOV2b	YTYLSTLYYECDPGYVLNGTERRTCQDDKNWDEDEPICIPVDCSSPPVVSANGQVRGDEYT	2847
	Q9ES77	-----	3567

	BAB55420	-----	1316
	AAH08135	-----	669
	Q9CUT3	-----	601
5	Q9H284	-----	481
	NOV2a	-----	3570
	NOV2b	FQKEIEYTCNEGFLLEGARSRVCLANGSWGATPDCVPVRCATPPQLANGVTEGLDYGFM	2907
	Q9ES77	-----	3567
10	BAB55420	-----	1316
	AAH08135	-----	669
	Q9CUT3	-----	601
	Q9H284	-----	481
	NOV2a	-----	3570
15	NOV2b	KEVTFHCHEGYILHGAPKLTCSQSDGNWDAEIPCKPVNCGPPEDLAHGFPNGFSFIHGGH	2967
	Q9ES77	-----	3567
	BAB55420	-----	1316
	AAH08135	-----	669
20	Q9CUT3	-----	601
	Q9H284	-----	481
	NOV2a	-----	3570
	NOV2b	IQYQCFPGYKLGHNSSRRCLSNWSGSSPCLPCRCSTPVIEYGTVNGTDFDCGKAARI	3027
25	Q9ES77	-----	3567
	BAB55420	-----	1316
	AAH08135	-----	669
	Q9CUT3	-----	601
	Q9H284	-----	481
30	NOV2a	-----	3570
	NOV2b	QCFKGFKLLGLSEITCEADGQWSSGFPHPCEHTSCGSLPMIPNAFISSETSSWKENVITYSC	3087
	Q9ES77	-----	3567
	BAB55420	-----	1316
35	AAH08135	-----	669
	Q9CUT3	-----	601
	Q9H284	-----	481
	NOV2a	-----	3570
40	NOV2b	RSGYVIQSSDLICTEKGWVSQPYPVCEPLSCGSPPSVANAVATGEAHTYESEVKLRCL	3147
	Q9ES77	-----	3567
	BAB55420	-----	1316
	AAH08135	-----	669
45	Q9CUT3	-----	601
	Q9H284	-----	481
	NOV2a	-----	3570
	NOV2b	GYTMDTDTDTFTCQKDGRWFPERISCSPPKCPENITHILVHGDDFSVNRQVSVSCAEG	3207
	Q9ES77	-----	3567
50	BAB55420	-----	1316
	AAH08135	-----	669
	Q9CUT3	-----	601
	Q9H284	-----	481
55	NOV2a	-----	3570
	NOV2b	YTFEGVNISVCQLDGTWEPPFSDESCSPVSCGKPESPEHGFVVGSKYTFESTIIYQCEPG	3267
	Q9ES77	-----	3567
	BAB55420	-----	1316

	AAH08135	-----	669
	Q9CUT3	-----	601
	Q9H284	-----	481
5	NOV2a	-----	3570
	NOV2b	YELEGNRERVQCENRQWSGGVAICKETRCETPLEFLNGKADIENRTTGPNVVYSCNRGYS	3327
	Q9ES77	-----	3567
	BAB55420	-----	1316
	AAH08135	-----	669
10	Q9CUT3	-----	601
	Q9H284	-----	481
	NOV2a	-----	3570
	NOV2b	LEGPSEAHCTENGTSHPVPLCKPNPCVPFVIPENALLSEKEYVDQNVSIKCREGFLN	3387
15	Q9ES77	-----	3567
	BAB55420	-----	1316
	AAH08135	-----	669
	Q9CUT3	-----	601
	Q9H284	-----	481
20	NOV2a	-----	3570
	NOV2b	QGHGIITCNPDETWTQTSACEKISCGPPAHVENAIARGVHYQYGDMITYSYSCYMGLEG	3447
	Q9ES77	-----	3567
	BAB55420	-----	1316
25	AAH08135	-----	669
	Q9CUT3	-----	601
	Q9H284	-----	481
	NOV2a	-----	3570
30	NOV2b	FLRSVCLENGTSWTSPPICRAVCRFPQNGGICQRPNACSCPEGWMGRLCEEPICILPCLN	3507
	Q9ES77	-----	3567
	BAB55420	-----	1316
	AAH08135	-----	669
	Q9CUT3	-----	601
35	Q9H284	-----	481
	NOV2a	-----	3570
	NOV2b	GGRCVAPYQCDPPGWTGSRCHTAVCQSPCLNGGKCVRPNRCHCLSSWTGHNCSRKRRTG	3567
	Q9ES77	-----	3567
40	BAB55420	-----	1316
	AAH08135	-----	669
	Q9CUT3	-----	601
	Q9H284	-----	481
45	NOV2a	-	3570
	NOV2b	F	3568
	Q9ES77	-	3567
	BAB55420	-	1316
	AAH08135	-	669
50	Q9CUT3	-	601
	Q9H284	-	481

Domain results for NOV2 were collected from the Pfam database, and then identified by the Interpro domain accession number. The results are listed in Table 2H with the statistics and domain description. These results indicate that the NOV2 polypeptides have properties similar to those of other proteins known to contain these domains.

5

Table 2H. Domain Analysis of NOV2			
PSSMs Producing Significant Alignments		Score (bits)	E Value
Von Willebrand Factor Type A (vwa): domain 1 of 1, from 80 to 256		86.8	4.5e-22
vwa	DivFLlDGsGsigsgnFervKdFvervverLdvgrprdkkeedavrVg		
NOV2a	+++ + + +++ + + ++++ +++ + + + ++ + ELVFLVDDSSSVGEVNFRELMEFVRKLLSDFPVVP-TA-----TRVA		
NOV2a	lvQYSdnvrtEikfklnyqnk.....devlqalqkiriedyygggg ++++ ++ + ++ ++ + ++ +++++ + +++ + ++ + +++ IVTFSSKNYV---VPRVDYISTrrarqhkcaLLLQEIPAI-----YRGGG		
NOV2a	tnTgaALqyvvrnlfteasGsRiepvaeegapkvlVvlTDGrsqddpspT + + + ++ + + + ++ +++++ ++ +++++ TYTKGAFQQAQILLH----AR-----ENSTKVFLITDGYSNGG----		
NOV2a	idirdvlnelkkeagvevfaiGvGnadnnnleeLreIAskpd.dhvfkvs + + ++++++ ++++++ + + + ++ + + + + + + ++ -DPRPIAASLRD-SGVEIFTFGIWQG-N--IRELNDMASTPKeEHCYLLH		
NOV2a	dfeaLdtlqell (SEQ ID NO:52) ++++ + +++++ SFEEFEALVALC (SEQ ID NO:6)		
pentaxin: domain 1 of 1, from 1469 to 1607		75.5	7.5e-21
Pentaxin	SYaTkKPlkDNEllifkekdqYslyvggaPqLevtfkvkeefvaPv		
NOV2a	++ + + + ++ +++++ +++ + + ++ SYAVDN-GSDNTLLL--TDYNGWVLYVNGR--EKITNCPSVNDGRWH		
NOV2a	HiCtSWeSssGiaeFWVDGkhCpwrkglkkGytvgaepsIiLGQEQDSy + + ++ +++ + ++ + HIAITWTSTGGAWRVYINGE-LSDGGTGLSIGKAIPGGGALVLGQEQDKK		
NOV2a	GGgFdksQSlVGEigdlNMDyVltPeeIktvykgagplerhiypNILdW (SEQ ID NO:53) + + + + + + + + + +++++ + + + + GEGFNPAESFVGSISQLNLWDYVLSPPQVKSLATS-CPEE-LSKGNVLAW (SEQ ID NO:6)		
sushi: domain 13 of 34, from 2145 to 2198		73.7	3.8e-18

sushi	Cp.pPdieNGrvsssgtyeypvGdtvtytCneGYrlvGsssitCted	
	+++ ++ + + + +++++ + ++ ++ ++++ ++ ++ ++	
NOV2a	CGePPSIMNGYASGS-NYSF--GAMVAYSCNKGfYIKGEKKSTCEAT	
	ggGgWsppllGelPkC	(SEQ ID NO:54)
	+ ++++ +	
NOV2a	--GQWSSPI----PTC	(SEQ ID NO:6)

The NOV2 disclosed in this invention is expressed in at least the following tissues:
adipose, adrenal gland, bone marrow, brain - amygdala, brain - cerebellum, brain - hippocampus,
brain - substantia nigra, brain - thalamus, brain - whole, fetal brain, fetal kidney, liver, lung, heart,
5 kidney, ascending colon, lymphoma - Raji, mammary gland/breast, pancreas, nasoepithelium,
pituitary gland, placenta, prostate, cervix, salivary gland, skeletal muscle, small intestine, spinal
cord, spleen, stomach, testis, thyroid, trachea, uterus. This information was derived by
determining the tissue sources of the sequences that were included in the invention including but
not limited to SeqCalling sources, Public EST sources, Literature sources, and/or RACE sources.

10 The protein similarity information, expression pattern, and map location for the Polydom-
like protein and nucleic acid disclosed herein suggest that this Polydom may have important
structural and/or physiological functions characteristic of the epidermal growth factor (EGF)
family. Therefore, the nucleic acids and proteins of the invention are useful in potential
diagnostic and therapeutic applications and as a research tool. For example, the compositions of
15 the presnet invention will have efficacy for treatment of patients suffering from: cancers,
congenital heart disease, inflammatory disorders, erythroid-megakaryocytic leukaemia,
Vacuoliting megalencephalic leukoencephalopathy, chronic contact dermatitis, fibrosarcoma,
wound healing, neoplasia, such as T-cell acute lymphoblastic leukemia/lymphoma, reproductive
disorders, fetal arrhythmias, immune system disorders, disorders of coagulation, obesity, diabetes,
20 asthma, arthritis, osteoporosis, and other diseases, disorders and conditions of the like.

The novel nucleic acid encoding the polydom-like protein of the invention, or fragments
thereof, are useful in diagnostic applications, wherein the presence or amount of the nucleic acid
or the protein are to be assessed. These materials are further useful in the generation of antibodies
that bind immunospecifically to the novel substances of the invention for use in therapeutic or
25 diagnostic methods. These antibodies may be generated according to methods known in the art,
using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies"

section below. The disclosed NOV2 protein has multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, a contemplated NOV2 epitope is from about amino acids 0 to 125. In another embodiment, a contemplated NOV2 epitope is from about amino acids 130 to 250. In other specific embodiments, contemplated NOV2 epitopes are from
5 about amino acids 250 to 3600.

NOV3

Another NOVX protein of the invention, referred to herein as NOV3, includes two novel transmembrane/IIIb-like protein. The disclosed proteins have been named NOV3a and NOV3b.
10 The NOV3a and NOV3b proteins of the invention cause growth inhibition of *E. coli* when expressed exogenously.

The NOV3a and NOV3b protein predicted here are localized extracellularly. Therefore, it is likely that they are accessible to a diagnostic probe, and for the various therapeutic applications described herein.

15 At least the NOV3b transmembrane-like protein disclosed in this invention maps to chromosome 20. This information was assigned using OMIM, the electronic northern bioinformatic tool implemented by CuraGen Corporation, public ESTs, public literature references and/or genomic clone homologies.

NOV3a

20 In one embodiment, a NOV3 variant is NOV3a (alternatively referred to herein as CG50273-01), which encodes a novel transmembrane-like protein and includes the 870 nucleotide sequence (SEQ ID NO:9) shown in Table 3A. An open reading frame for the mature protein was identified beginning with an ATG codon at nucleotides 1-3 and ending with a TAA codon at
25 nucleotides 628-630. Putative untranslated regions downstream from the termination codon and upstream from the initiation codon are underlined in Table 3A, and the start and stop codons are in bold letters.

Table 3A. NOV3a Nucleotide Sequence (SEQ ID NO:9)

ATGGGGCTCCTGCTCCGGCCGCTGCGCGCTCGTCGTCCTCTGCGCTTTTCAGCTGGTGGTGGCCGCTGGAGAGGC
 AGGTGTTTGAATTCCTGGGCTACCACTGGGCGCCATCCTGGCCAACCTTGTCCACATCATCATCGTCATCCTGGG
 ACTCTTCGGCACCATCCAGTACCGGCTGCGCTATGTCATGGTGTACACGCTGTGGGCAGCCGTCTGGGTCACCTGG
 AACGTCTTCATCATCTGCTTCTACCTGGAAGTCGGTGGCCTCTTAAAGGACAGCGAGCTACTGACCTTCAGCCTCT
 CCCGGCATCGCTCCTGGTGGCGTGAGCGCTGGCCAGGCTGTCTGCATGAGGAGGTGCCAGCAGTGGGCCTCGGGGC
 CCCCCATGGCCAGGCCCTGGTGTGAGGTGCTGGCTGTGCCCTGGAGCCCAGCTATGTGGAGGCCCTACACAGTTGC
 CTGCAGATCCTGATCGCGCTTCTGGGCTTTGTCTGTGGCTGCCAGGTGGTCAAGCGTGTTCACGAGGAAGAGGACA
 GCTTTGATTTTCATTGGTGGATTGATCCATTTCTCTCTACCATGTCAATGAAAAGCCATCCAGTCTCTTGTCCTAA
 GCAGGTGTACTTGCCGCGTAAGTGAGGAAACAGCTGATCCTGCTCCTGTGGCCTCCAGCCTTCAGCGACCGACCA
 GTGACAATGACAGGAGCTCCCAGGCCTTGGGACGCGCCCCACCCAGCACCCCCAGGCGGCCGGCAGCACCTGCC
 CTGGGTTTAAAGTACTGGACACCAGCCAGGGCGGCAGGGCAGTGCCACGGCTGGCTGCAGCGTCAAGAGAGTTTGT
 AATTCCTTTCTCTTAAAAAAAAAAAAAAAAAAAAA

The sequence of NOV3a was derived by laboratory cloning of cDNA fragments, by *in silico* prediction of the sequence. The cDNA fragments covering either the full length of the DNA sequence, or part of the sequence, or both, were cloned. *In silico* prediction was based on sequences available in CuraGen's proprietary sequence databases or in the public human sequence databases, and provided either the full length DNA sequence, or some portion thereof.

The DNA sequence and protein sequence for a novel transmembrane-like gene were obtained by SeqCalling™ Technology and are reported here as NOV3a. These methods used to amplify NOV3a cDNA are described in Example 2.

The NOV3a polypeptide (SEQ ID NO:10) encoded by SEQ ID NO:9 is 209 amino acid residues in length and is presented using the one-letter amino acid code in Table 3B. The SignalP, Psort and/or Hydropathy results predict that NOV3a has a signal peptide and is likely to be localized extracellularly at the plasma membrane with a certainty of 0.4600. In alternative embodiments, a NOV3a polypeptide is located to the microbody (peroxisome) with a certainty of 0.1026, the endoplasmic reticulum (membrane) with a certainty of 0.1000, or the endoplasmic reticulum (lumen) with a certainty of 0.1000. The SignalP predicts a likely cleavage site for a NOV3a peptide between amino acid positions 29 and 30, i.e. at the dash in the sequence GAG-VL.

Table 3B. Encoded NOV3a Protein Sequence (SEQ ID NO:10)

MGSCSGRCALVVLCAFLVVAALERQVFDFLG YQWAPILANFVHIIIVILGLFGTTIQYRLRYVMVYTLWAAVWVTW
 NVFIICFYLEVGGLLKDSSELLTFSLSRHRSWWRERWPGCLHEEVPVAVGLGAPHGQALVSGAGCALEPSYVEALHSC
 LQILIALLLGFVCGCQVVSVFTEEDSFDFIGGFDPFPLYHVNEKPSSLLSKQVYLP

NOV3b

In an alternative embodiment, a NOV3 variant is NOV3b (alternatively referred to herein as CG50273-02), which includes the 632 nucleotide sequence (SEQ ID NO:11) shown in Table 3C. An open reading frame for the mature protein was identified beginning with an GTC codon at nucleotides 2-4 and ending with a TAA codon at nucleotides 593-595. The start and stop codons of the open reading frame are highlighted in bold type. Putative untranslated regions are underlined and found upstream from the initiation codon and downstream from the termination codon.

Table 3C. NOV3b Nucleotide Sequence (SEQ ID NO:11)

CGTCCTCTGCGCTTTTCAGCTGGTCGCCGCCCTGGAGAGGCAGGTGTTTGACTTCCTGGGCTACCACTGGGCGCC
 CATCCTGGCCAACCTTTGTCCACATCATCATCGTCATCTGGGACTCTTCGGCACCATCCAGTACCGGCTGCGCTA
 TGTTCATGGTGTACACGCTGTGGGCAGCCGTCTGGGTACCTGGAACGTCTTCATCATCTGCTTCTACCTGGAAGT
 CGGTGGCCTCTTAAAGGACAGCGAGCTACTGACCTTCAGCCTCTCCGGCATCGCTCCTGGTGGCGTGAGCGCTG
 GCCAGGCTGTCTGCATGAGGAGGTGCCAGCAGTGGGCCTCGGGGCCCCCATGGCCAGGCCCTGGTGTCAAGTGC
 TGGCTGTGCCCTGGAGCCAGCTATGTGGAGGCCCTACACAGTTGCCTGCAGATCCTGATCGCGCTTCTGGGCTT
 TGTCTGTGGCTGCCAGGTGGTTCAGCGTGTTCACGGAGGAAGAGGACAGCTTTGATTTCATTGGTGGATTGATCC
 ATTTCTCTCTACCATGTCAATGAAAAGCCATCCAGTCTCTTGTCCAAGCAGGTGTACTTGCCTGCGTAAGTGA
GAAACAGCTGATCCTGCTCCTGTGGCCTCCAC

The sequence of NOV3b was derived by laboratory cloning of cDNA fragments, by *in silico* prediction of the sequence. The cDNA fragments covering either the full length of the DNA sequence, or part of the sequence, or both, were cloned. *In silico* prediction was based on sequences available in CuraGen's proprietary sequence databases or in the public human sequence databases, and provided either the full length DNA sequence, or some portion thereof.

The cDNA coding for the NOV3b sequence was cloned by the polymerase chain reaction (PCR). Primers were designed based on *in silico* predictions of the full length or some portion (one or more exons) of the cDNA/protein sequence of the invention, or by translated homology of the predicted exons to closely related human sequences or to sequences from other species. The DNA sequence and protein sequence for a novel transmembrane-like gene were obtained by exon linking and are reported here as NOV3b. These primers and methods used to amplify NOV3b cDNA are described in Example 2.

The NOV3b polypeptide (SEQ ID NO:12) encoded by SEQ ID NO:11 is 197 amino acid residues in length and is presented using the one-letter amino acid code in Table 3D. The

SignalP, Psort and/or Hydropathy results predict that NOV3b has a signal peptide and is likely to be localized in the membrane of the endoplasmic reticulum with a certainty of 0.6850. In alternative embodiments, a NOV3b polypeptide is located to the plasma membrane with a certainty of 0.6400, the Golgi body with a certainty of 0.4600, or the endoplasmic reticulum (lumen) with a certainty of 0.1000. The SignalP predicts a likely cleavage site for a NOV3b peptide between amino acid positions 13 and 14, i.e. at the dash in the sequence LER-QV.

Table 3D. Encoded NOV3b Protein Sequence (SEQ ID NO:12)

VLCAFQLVAALERQVFDFLGYQWAPILANFVHIIIVILGLFGTIQYRLRYVMVYTLWAAVWVTWNVFIICFYLEVGLLLKDSSELLTFSLSRHRSWWRERWPGCLHEEVPAVGLGAPHGQALVSGAGCALEPSYVEALHSCLOILIALLGFCGCQVVSVFTEEDSFDFIGGFDPFPLYHVNEKPSSLLSKQVYLP

SNP variants of NOV3 are disclosed in Example 3.

NOV3 Clones

Unless specifically addressed as NOV3a or NOV3b, any reference to NOV3 is assumed to encompass all variants.

The amino acid sequence of NOV3 has high homolgy to other proteins as shown in Table 3E.

Table 3E. BLASTX Results from Patp Database for NOV3

		High Score	Smallest Sum Prob P
Sequences Producing High-Scoring Segment Pairs:			
patp:AAB62810	Human nervous system associated protein NSPRT3	1092	2.3e-110
patp:AAY94954	Human secreted protein clone iw66_1	619	3.0e-60
patp:AAG78000	Human actin 14	466	4.9e-44
patp:AAB94211	Human protein sequence	425	1.1e-39
patp:AAB25811	Human secreted protein	317	3.0e-28

In a search of sequence databases, it was found, for example, that the NOV3a nucleic acid sequence has 572 of 704 bases (81%) identical to a gb:GENBANK-

ID:AB030182|acc:AB030182.1 mRNA from Mus musculus (Mus musculus mRNA, complete cds, clone:1-107). Further, the full amino acid sequence of the protein of the disclosed NOV3a

protein of the invention has 173 of 209 amino acid residues (82%) identical to, and 182 of 209 amino acid residues (87%) similar to, the 208 amino acid residue ptrn:SPTREMBL-ACC:Q9JMG4 protein from *Mus musculus* (Mouse) (MRNA, COMPLETE CDS, CLONE:1-107).

5 In a similar search of sequence databases, it was found, for example, that the NOV3b nucleic acid sequence has 514 of 618 bases (83%) identical to a gb:GENBANK-ID:AB030182|acc:AB030182.1 mRNA from *Mus musculus* (*Mus musculus* mRNA, complete cds, clone:1-107). Further, the full amino acid sequence of the disclosed NOV3b protein of the invention has 165 of 196 amino acid residues (84%) identical to, and 173 of 196 amino acid
10 residues (88%) similar to, the 208 amino acid residue ptrn:SPTREMBL-ACC:Q9JMG4 protein from *Mus musculus* (Mouse) (MRNA, COMPLETE CDS, CLONE:1-107).

Additional BLASTP results are shown in Table 3F.

Table 3F. NOV3 BLASTP Results

Gene Index/ Identifier	Protein/Organism	Length of aa	Identity (%)	Positives (%)	Expect Value
Q9BQU8	BA261N11.2.1 (NOVEL PROTEIN, ISOFORM 1) - <i>Homo sapiens</i>	207	207/209 (99%)	207/209 (99%)	1.4e-110
Q9JMG4	MRNA, COMPLETE CDS, CLONE:1-107 (C030019F02RIK, PROTEIN) - <i>Mus musculus</i> (Mouse)	208	173/209 (82%)	182/209 (87%)	1.0e-91
Q9D8W0	C030019F02RIK PROTEIN - <i>Mus musculus</i> (Mouse)	208	172/209 (82%)	181/209 (86%)	3.5e-91
Q9D1V9	C030019F02RIK PROTEIN - <i>Mus musculus</i> (Mouse)	208	172/209 (82%)	181/209 (86%)	3.5e-91
Q9D0Q6	2610200G18RIK PROTEIN - <i>Mus musculus</i> (Mouse)	207	120/206 (58%)	144/206 (69%)	8.0e-60

15 A multiple sequence alignment is given in Table 3G, with the NOV3 protein of the invention being shown in lines 1 and 2, in a ClustalW analysis comparing NOV3 with related protein sequences of Table 3F.

Table 3G. ClustalW Analysis of NOV3

20

1. SEQ ID NO.: 10	NOV3a	5. SEQ ID NO.: 57	Q9D8W0
2. SEQ ID NO.: 12	NOV3b	6. SEQ ID NO.: 58	Q9D1V9

3. SEQ ID NO.: 55
4. SEQ ID NO.: 56

Q9BQU8
Q9JMG4

7. SEQ ID NO.: 59

Q9D0Q6

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5
NOV3a  MGSCSGRCALVVLCAFQLVVAALERQVFDFLGYQWAPILANFVHIIIVILGLFGTIQYRL 60
NOV3b  -----VLCAFQL-VAALERQVFDFLGYQWAPILANFVHIIIVILGLFGTIQYRL 48
Q9BQU8  MGSCSGRCALVVLCAFQL-VAALERQVFDFLGYQWAPILANFVHIIIVILGLFGTIQYRL 59
10 Q9JMG4  MGFCSGRCTLLALCALQL-VTALERQVFDFLGYQWAPILANFTHIIVVILGLFGTIQYRP 59
Q9D8W0  MGFCSGRCTLLALCALQL-VTALERQVFDFLGYQWAPILANFTHIIVVILGLFGTIQYRP 59
Q9D1V9  MGFCSGRCTLLALCALQL-VTALERQVFDFLGYQWAPILANFTHIIVVILGLFGTIQYRP 59
Q9D0Q6  MGKCSGRCCTLVAFCCQL-VAALQRQIFDFLGYQWAPILANFHHIMAVILGTFGTQYRS 59

15 NOV3a  RYVMVYTLWAAVWVTWNVFIICFYLEVGGGLKDSE-LLTFSLSRHRSWWRERWPGCLHEE 119
NOV3b  RYVMVYTLWAAVWVTWNVFIICFYLEVGGGLKDSE-LLTFSLSRHRSWWRERWPGCLHEE 107
Q9BQU8  RYVM-VYTLWAAVWVTWNVFIICFYLEVGGGLKDSE-LLTFSLSRHRSWWRERWPGCLHEE 117
Q9JMG4  RYIVVYVWAAVWVTWNVFIICFYLEVGGGLSKDSE-LLTFNLSGHRSWWEHGPCLHEE 118
Q9D8W0  RYIVVYVWAAVWVTWNVFIICFYLEVGGGLSKDSE-LLTFNLSGHRSWWEHGPCLHEE 118
Q9D1V9  RYIVVYVWAAVWVTWNVFIICFYLEVGGGLSKDSE-LLTFNLSGHRSWWEHGPCLHEE 118
20 Q9D0Q6  RYLILYAANLVLVVGVNNAFIICFYLEVGGGLSKDSE-LLTFNLSGHRSWWEHGPCLVTP 119

NOV3a  VPAVGLGAPHGQALVSGAGCALEPSYVEALHSCLQIILALLGFVCGCQVVSVFTEEDSF 179
NOV3b  VPAVGLGAPHGQALVSGAGCALEPSYVEALHSCLQIILALLGFVCGCQVVSVFTEEDSF 167
25 Q9BQU8  VPAVGLGAPHGQALVSGAGCALEPSYVEALHSCLQIILALLGFVCGCQVVSVFTEEDSF 177
Q9JMG4  EATAGLGALHGQSLVVGAGCAMVHSYVEALHSGLQIILALLGFVYGCYVVSVLTEEDSF 178
Q9D8W0  EATAGLGALHGQSLVVGAGCAMVHSYVEALHSGLQIILALLGFVYGCYVVSVLTEEDSF 178
Q9D1V9  EATAGLGALHGQSLVVGAGCAMVHSYVEALHSGLQIILALLGFVYGCYVVSVLTEEDSF 178
Q9D0Q6  VLNSRL-ALEDHHVTSVTGCLLDYPYIEALSSALQIFLALGFVFACVYSKVFLEEDSF 178

30 NOV3a  DFIGGFDPFPLYHVNEKPSSLLSKQVYLP 209
NOV3b  DFIGGFDPFPLYHVNEKPSSLLSKQVYLP 197
Q9BQU8  DFIGGFDPFPLYHVNEKPSSLLSKQVYLP 207
Q9JMG4  DFIGGFDPFPLYHVNEKPSSLLSKQAYLP 208
Q9D8W0  DFIGGFDPFPLYHVNEKPSSLLSKQAYLP 208
35 Q9D1V9  DFIGGFDPFPLYHVNEKPSSLLSKQAYLP 208
Q9D0Q6  DFIGGFDSYG-YQAPQKTSHLQLQPLYTSG 207

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In a search of the Pfam database, there were no known domain results for NOV3.

40 The NOV3 disclosed in this invention is expressed in at least the following tissues: bone marrow, brain - substantia nigra, brain - temporal lobe, brain - whole, heart, kidney, pancreas, astrocytoma, CNS, multiple sclerosis lesions, and uterus. This information was derived by determining the tissue sources of the sequences that were included in the invention including but not limited to SeqCalling sources, Public EST sources, Literature sources, and/or RACE sources.

45 The protein similarity information, expression pattern, and map location for the transmembrane-like protein and nucleic acid disclosed herein suggest that this protein may have important structural and/or physiological functions characteristic of the transmembrane family. Therefore, the nucleic acids and proteins of the invention are useful in potential diagnostic and

therapeutic applications and as a research tool. For example, the compositions of the present invention will have efficacy for treatment of patients suffering from: cancer, trauma, regeneration (in vitro and in vivo), viral/bacterial/parasitic infections, neuroprotection, Von Hippel-Lindau (VHL) syndrome, Alzheimer's disease, stroke, tuberous sclerosis, hypercalcaemia, Parkinson's disease, Huntington's disease, cerebral palsy, epilepsy, Lesch-Nyhan syndrome, multiple sclerosis, ataxia-telangiectasia, leukodystrophies, behavioral disorders, addiction, anxiety, pain and other diseases, disorders and conditions of the like.

The novel nucleic acid encoding the transmembrane-like protein of the invention, or fragments thereof, are useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed. These materials are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. The disclosed NOV3 protein has multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, a contemplated NOV3 epitope is from about amino acids 85 to 130. In another embodiment, a contemplated NOV3 epitope is from about amino acids 165 to 210.

NOV4

Still another NOVX protein of the invention, referred to herein as NOV4 (alternatively referred to as CG50289-01), is a serine protease-like protein.

Proteolytic enzymes that exploit serine in their catalytic activity are ubiquitous, being found in viruses, bacteria and eukaryotes. They include a wide range of peptidase activity, including exopeptidase, endopeptidase, oligopeptidase and omega-peptidase activity. Over 20 families of serine protease have been identified and although they have different evolutionary origins, there are similarities in the reaction mechanisms of several peptidases. Chymotrypsin, subtilisin and carboxypeptidase C clans have a catalytic triad of serine, aspartate and histidine in common: serine acts as a nucleophile, aspartate as an electrophile, and histidine as a base. The geometric orientations of the catalytic residues are similar between families, despite different protein folds. The enzymes are inherently secreted, being synthesised with a signal peptide that

targets them to the secretory pathway. Animal enzymes are either secreted directly, packaged into vesicles for regulated secretion, or are retained in leukocyte granules.

Although SignalP, Psort and/or hydropathy suggest that the Serine Protease-like protein may be localized at the plasma membrane, the protein predicted here is similar to the Serine

5 Protease family, some members of which are secreted. Therefore it is likely that this novel Serine Protease-like protein is available at the same sub-cellular localization and hence accessible to a diagnostic probe and for various therapeutic applications.

The NOV4 nucleic acid and polypeptide described in this application has a structure similar to Testicular Serine Protease-1 (TESP-1) and TESP-2, serine proteases isolated from the
10 mouse sperm acrosome. These proteins may play a role in fertilization and/or processing of other proteins during fertilization.

The NOV4 protein disclosed in this invention maps to chromosome 2. This information was assigned using OMIM, the electronic northern bioinformatic tool implemented by CuraGen Corporation, public ESTs, public literature references and/or genomic clone homologies.

15 The NOV4 nucleic acid (SEQ ID NO:13) of 909 nucleotides encodes a novel serine protease-like protein and is shown in Table 4A. An open reading frame for the mature protein was identified beginning with a ATG initiation codon at nucleotides 14-16 and ending with a TGA codon at nucleotides 899-901. Putative untranslated regions upstream from the start codon and downstream from the termination codon are underlined in Table 4A. The start and stop
20 codons are in bold letters.

Table 4A. NOV4 Nucleotide Sequence (SEQ ID NO:13)

<p> <u>GGCCACCGGCCTGATGAGGGAAGCAGGGGCAGAGCGCTCAGGCCAGCCGGCGGGGGCACTGCGCACTGGCCGCCTC</u> CCTCCTCTGGCCAATCCTCCTGCCGCTGCGCGTCTAGTCCACCTCGTCCCTCTCTGCAGGTCCACTAACCCATCTG ATTACCGGATCCTGCTTGGGTATGACCAGCAAAGCCATCCCACAGAGCACAGCAAGCAGATGACAGTGAATAAGAT CATGGTGCACGCTGACTATAACGAGTTGCACCGCATGGGGAGTGACATCACCTGCTGCAGCTGCACCGTCATGTG GAATTGAGCTCCACATCCTCCCCGCCTGCCTTCCGGAACCAACCACGTGGCTGGCCCTGACAGCTCCTGCTGGA TATCTGGTTGGGGAATGGTCACCGAGGATGTCTTCTGCTGAGCCCTTCCAACCTTCAGGAGGCAGAGGTCGGTGT CATGGACAACACTGTCTGCGGATCCTTTTTCCAGCCCCAGTACCCCCGCCAGCCAAGCAGCAGTGACTACACCATC CACGAGGACATGCTGTGCGCTGGGGACCTCATAACAGGAAAGGCCATTGCGGACGAGACTCCAGGGGTCCCCTCG TCTGCCCATTAAATGGCACCTGGTTCTGATGGGGCTGTCTAGTTGGAGCCTCGACTGCTGCTCACCCGTCGGTCC CAGGGTCTTACACAGGCTCCCCTACTTCACCAACTGGATCAGCCAGAAGAAGAGGGAGAGCACCCCTCCAGATCCC GCCTTGGCTCCTCCTCAGGAAACACCCCCAGCCCTGGACAGCATGACCTCTCAGGGCATCGTCCACAAGCCCCGGGC TCTGCGCAGCCCTTCTGGCTGCTCACATGTTCTCTGCTGCTGATTCTCTCTGGGGAGCCTGTGAAGGGCCAG </p>

The sequence of NOV4 was derived by laboratory cloning of cDNA fragments covering the full length and/or part of the DNA sequence of the invention, and/or by *in silico* prediction of the full length and/or part of the DNA sequence of the invention from public human sequence databases.

The DNA sequence and protein sequence for a novel polydom-like gene were obtained by SeqCalling™ Technology and are reported here as NOV4. These methods used to amplify NOV4 cDNA are described in Example 2.

The NOV4 polypeptide (SEQ ID NO:14) encoded by SEQ ID NO:13 is 295 amino acid residues in length and is presented using the one-letter amino acid code in Table 4B. The SignalP, Psort and/or Hydropathy results predict that NOV4 has no known signal peptide and is likely to be localized in the endoplasmic reticulum membrane with a certainty of 0.8500. In alternative embodiments, a NOV4 polypeptide is located to the plasma membrane with a certainty of 0.4400, the microbody (peroxisome) with a certainty of 0.3313, or the mitochondrial inner membrane with a certainty of 0.1000.

Table 4B. Encoded NOV4 Protein Sequence (SEQ ID NO:14)

MREAGAERSGQAGALRTGRLPPLANPPAAARLVHLVPLCRSTNPSDYRILLGYDQQSHPTTEHSKQMTVNMIMVH
ADYNELHRMGSDITLLQLHRHVEFSSHILPACLPEPTTWLAPDSSCWISGWMVTEDEVFLPEPFQLQEAIEVGVM
NTVCGSFFQPPQYGPQSSDYTIHEDMLCAGDLITGKAICRRDSRGPLVCPLNGTWFLMGLSSWSLDCCSPVGPR
VFTRLPYFTNWISQKKRESTPPDPALAPPQETPPALDSMTSQGIVHKPGLCAALLAAHMFLLLLILLGSL

SNP variants of NOV4 are disclosed in Example 3.

The amino acid sequence of NOV4 has high homology to other proteins as shown in Table 4C.

Table 4C. BLASTX Results from Patp Database for NOV4

Sequences Producing High-Scoring Segment Pairs:		High Score	Smallest Sum Prob P (N)
patp:AAW64239	Gerbil homologue of mouse mMCP-7 zymogen – Meriones	344	4.2e-31
patp:AAW64240	Human mast cell tryptase II/beta	342	6.8e-31
patp:AAW64241	Human mast cell tryptase III	342	6.8e-31
patp:AAW63175	Human mast cell tryptase II/beta polypeptide	342	6.8e-31
patp:AAW63176	Human mast cell tryptase III polypeptide	342	6.8e-31

In a search of sequence databases, it was found, for example, that the NOV4 nucleic acid sequence has 583 of 885 bases (65%) identical to a gb:GENBANK-

ID:AB008910|acc:AB008910.1 mRNA from *Mus musculus* (*Mus musculus* mRNA for TESP1,

complete cds). Further, the full amino acid sequence of the disclosed NOV4 protein of the

5. invention has 120 of 253 amino acid residues (47%) identical to, and 172 of 253 amino acid residues (67%) similar to, the 367 amino acid residue ptnr:SPTREMBL-ACC:O70169 protein from *Mus musculus* (Mouse) (TESTICULAR SERINE PROTEASE 1 (TESP1)).

Additional BLASTP results are shown in Table 4D.

Table 4D. NOV4 BLASTP Results

Gene Index/ Identifier	Protein/Organism	Length of aa	Identity (%)	Positives (%)	Expect Value
O70169	TESTICULAR SERINE PROTEASE 1 (TESP1) - <i>Mus musculus</i> (Mouse)	367	120/253 (47%)	172/253 (67%)	2.1e-59
O70170	TESTICULAR SERINE PROTEASE 2 (TESP2) - <i>Mus musculus</i> (Mouse)	366	120/252 (47%)	157/252 (62%)	4.0e-58
Q9D9S6	TESTICULAR SERINE PROTEASE 2 - <i>Mus musculus</i> (Mouse)	143	69/140 (49%)	90/140 (64%)	4.5e-34
Q9XSM2	Tryptase 2 precursor (EC 3.4.21.59) - <i>Ovis aries</i> (Sheep)	273	72/195 (36%)	112/195 (57%)	7.6e-32
Q9XSM1	TRYPTASE (EC 3.4.21.59) - <i>Ovis aries</i> (Sheep)	273	73/195 (37%)	112/195 (57%)	9.7e-32

A multiple sequence alignment is given in Table 4E in a ClustalW analysis comparing NOV4 with related protein sequences disclosed in Table 4D.

Table 4E. ClustalW Analysis of NOV4

- | | | | |
|-------------------|--------|-------------------|--------|
| 1. SEQ ID NO.: 14 | NOV4 | 4. SEQ ID NO.: 62 | Q9D9S6 |
| 2. SEQ ID NO.: 60 | O70169 | 5. SEQ ID NO.: 63 | Q9XSM2 |
| 3. SEQ ID NO.: 61 | O70170 | 6. SEQ ID NO.: 64 | Q9XSM1 |

NOV4	MREAGAERSGQP-----AGALRTGRLP-----PLANPPAAARLVHLVP-----	38
O70169	MWGSRAQQSGPDRGGACLLAFLLCFSLHAQDYTPSQTPPPTSNTSLKPRGR-----	53
O70170	MCGVRAKKSGLSGYGAGLLAALLGVSFLLS-----QHAQTAEPTNVTNAANNTTIQIMKST	55
Q9D9S6	-----	1
Q9XSM2	-----MLHLLALALLLS-----LVSAAPAPGQALQSG-----	28

	QPXSM1	-----MLHLIALALILS-----LVSAAPGPGQALQRS-----	28
	NOV4	-----	38
5	O70169	-VQKELCGKTKFQGKIYGGQIAKAERWPWQASLIF---RGRHICGAVLIDKTWLLSAAHC	109
	O70170	LSLSEVCGKTKFQGKIYGGQIAGAERWPWQASRL---YGRHICGAVLIDKNWVLGAHC	112
	Q9D9S6	-----	1
	Q9XSM2	-----IIIGGKEAPGSRWPWQVSLRVRDQYWRHQCGGSLIHPQWVLTAAHC	73
	QPXSM1	-----IIIGGKEAPGSRWPWQVSLRVRDQYWRHQCGGSLIHPQWVLTAAHC	73
10	NOV4	LCRST-NPSDYRILLGYDQOSHPTTEHSKOMTVNKLIMVHADYNELHRMGSDITLLQLHRHV	97
	O70169	FQPSL-TPSDYRILLGYNQLSNPSNYSROMTVNKLIMVHADYNELHRMGSDITLLQLHRHV	168
	O70170	FQRSQ-EPSPDHVMLGYTDLNSPTRYSRITMSVQKVIVEKDYNRFTQGSDIVLLQLRSSV	171
	Q9D9S6	-----MLGYTDLNSPTRYSRITMSVQKVIVEKDYNRFTQGSDIVLLQLRSSV	47
	Q9XSM2	IGPELQEPSPDFRVQVLRQHLYYQD---RLIPISRVIPHPHYMVEN-GADIALLOLEEV	129
15	QPXSM1	IGPELQEPSPDFRVQVLRQHLYYQD---RLIPISRVIPHPHYMVEN-GADIALLOLEEV	129
	NOV4	EFSSHILPACLPPEPTTWLAPDSSCWISGWMVTEDVFLPEPFQLEAEVGVMDNTVCGSF	157
	O70169	IYSTHIFPACVDPDGTTKVSPNNLCWISGWMVSADKFLQAPFLLDAEVSLIDEEECTTF	228
20	O70170	EYSSHILPACVPEENIKIPKEKACWASGWCYLREDVRIPLPNELYEABITIMSNDQCKGF	231
	Q9D9S6	EYSSHILPACVPEENIKIPKEKACWASGWCYLREDVRIPLPNELYEABITIMSNDQCKGF	107
	Q9XSM2	SISRHVQPVTLPPASETFPPESQCWVTGWGDVNGRPLPPPYPLKQVKVPIVENSVCWDK	189
	QPXSM1	SISCHVREVTLPASETFPPESQCWVTGWGDVNGRPLPPPYPLKQVKVPIVENSVCWDK	189
25	NOV4	FQPYPGQPSSSDYTIHEDMLCAGDLITGKATCRRDSRGPLVCPNLGTWFLMGLSSWSLD	217
	O70169	FQTPEVS---ITEYDVIKDDVLCAGDLTNQKSSCRGDSGGPLVCFNLGFWVVGIANWGA	286
	O70170	FPPPVPG---SSRSYIYDDMVCAADYDMSKSTICAGDSGGPLVCLLEGSWYVVGLTWSST	289
	Q9D9S6	FPPPVPG---SGRSYIYDDMVCAADYDMSKSTICAG-----LLL-----	143
	Q9XSM2	YHSGLIST--DYSVPVIVQEDNLCAGD--GGRDSCQDSSGGPLVCKVNGTWLQAGVVSWDG	245
30	QPXSM1	YHSGLIST--DYSVPVIVQEDNLCAGD--GGRDSCQDSSGGPLVCKVNGTWLQAGVVSWDG	245
	NOV4	CCSPVG-PRVFTRLPYFTNWISQKKRESTPPDPALAPPQETPPALDS---MTSQGIVHK	272
	O70169	CLEPIHSPNIFTKVSYFSDWIKQKKANTPAADVSSAPLEEMASSLRG--WGNYSAGITLK	344
	O70170	CEEPVSPSVFARVSYFDKWKDKNKKSSSNSKPGESPHHPGSPENENPEGNNKNQGTVIK	349
	Q9D9S6	-----	143
35	Q9XSM2	CAKPNR-PGTYTRITSYLDWIHQYVPQEP-----	273
	QPXSM1	CANPDY-PGVYTRITSYLDWIHQYVPQEP-----	273
	NOV4	PGLCAALLAAHMFLLLLLILGSL	295
	O70169	PRISTTLLSSQALLLQSIWLRIL	367
40	O70170	P-VCTALLSQTLQLQLI-----	366
	Q9D9S6	-----	143
	Q9XSM2	-----	273
	QPXSM1	-----	273

45

50

Domain results for NOV4 were collected from the Pfam database, and then identified by the Interpro domain accession number. The results are listed in Table 4F with the statistics and domain description. These results indicate that the NOV4 polypeptide has properties similar to those of other proteins known to contain these domains.

Table 4F. Domain Analysis of NOV4		
PSSMs Producing Significant Alignments		Score (bits)
trypsin: domain 1 of 1, from 42 to 237		E Value
Trypsin	sapassvrVSlsvrlGehnlsltegteqkfdvkkttiivHpnyndt. ++ ++++++ + ++ +++ + +++++ + + +++ +	119.2
NOV4	STNPSDYRI----LLGYDQQSHPTTEHSKQMTVNK-IMVHADYNELHr	5.3e-37
NOV4	ldngaYdnDiAlLkLkspgvtlgtvvpicLpsassdlpvGttctvsGwG ++ ++++++ + ++ + ++++++ +++ +++ ++++++ + MG-----SDITLLQLHRH-VEFSSHILPACLPEPTTWLAPDSSCWISGWG	
NOV4	rrptknlgl...lsdtLqevvvpvvsretCrsaye..ygggt.....dDkv + ++ + + + ++++++ + + ++++++ ++++++ + M--VTEDVflpEPFQLQEAEGVMDNTVCGSFFQpQYPGQpssdyT---	
NOV4	efvtdnmiCagal.ggkdaCqGDSGGPLvcsgnrdgrwelvGivSwGsy + +++++ ++ + +++++ + +++ + ++++++ ++ --IHEDMLCAGDLiTGKAICRRDSRGPLVCPLN---GTWFLMGLSSWS-L	
NOV4	gCargnkPGvytrVssyldWI (SEQ ID NO:65) ++ +++++ ++ + DCCSPVGPRVFTRLPYFTNWI (SEQ ID NO:14)	

The Serine Protease disclosed in this invention is expressed in at least the following tissues: testis. This information was derived by determining the tissue sources of the sequences that were included in the invention.

The protein similarity information, expression pattern, and map location for the serine protease-like protein and nucleic acid disclosed herein suggest that this protein may have important structural and/or physiological functions characteristic of the serine protease family. Therefore, the NOV4 nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications and as a research tool. For example, the compositions of the present invention will have efficacy for treatment of patients suffering from: cancer, trauma, regeneration (in vitro and in vivo), viral/bacterial/parasitic infections, infertility and other diseases, disorders and conditions of the like.

The novel nucleic acid encoding the serine protease-like protein of the invention, or fragments thereof, are useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed. These materials are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in

therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. The disclosed NOV4 protein has multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, a contemplated NOV4 epitope is from about amino acids 10 to 30. In another embodiment, a contemplated NOV4 epitope is from about amino acids 35 to 40. In other specific embodiments, contemplated NOV4 epitopes are from about amino acids 45 to 90, 105 to 112, 115 to 120, 127 to 145, 152 to 180, 180 to 195, and 225 to 265.

10 NOV5

A further NOVX protein of the invention, referred to herein as NOV5, includes two novel Wnt-7a-like proteins. The disclosed proteins have been named NOV5a and NOV5b.

Wnt proteins constitute a large family of molecules involved in cell proliferation, cell differentiation and embryonic patterning. They are known to interact with the Frizzled family of receptors to activate two main intracellular signaling pathways regulating intracellular calcium levels and gene transcription. Wnts play a role in cell proliferation and tumorigenesis, and are also involved in processes involved in mammary gland development and cancer. Furthermore, Wnts are critical to organogenesis of several systems, such as the kidney and brain. Wnts regulate the early development, *i.e.* neural induction, and their role persists in later stages of development as well as in the mature organ.

The NOV5 proteins predicted here are localized extracellularly. Therefore, it is likely that these Wnt-7a-like proteins are accessible to a diagnostic probe, and for the various therapeutic applications described herein.

At least the NOV5a protein disclosed in this invention maps to chromosome 3. This information was assigned using the electronic northern bioinformatic tool implemented by CuraGen Corporation, public ESTs, public literature references and/or genomic clone homologies.

NOV5a

In one embodiment, a NOV5 variant is NOV5a (alternatively referred to herein as CG50353-01), which encodes a novel Wnt-7a-like protein and includes the 1628 nucleotide sequence (SEQ ID NO:15) shown in Table 5A. An open reading frame for the mature protein was identified beginning with a ATG initiation codon at nucleotides 1-3 and ending with a TGA

codon at nucleotides 1048-1050. Putative untranslated regions upstream from the start codon and downstream from the termination codon are underlined in Table 5A. The start and stop codons are in bold letters.

5

Table 5A. NOV5a Nucleotide Sequence (SEQ ID NO:15)

ATGAACCGGAAAGCGCGGCGCTGCCTGGGCGACCTCTTTCTCAGCCTGGGCATGGTCTGTCTCCTAGCATGTGGC
 TTCTCCTCAGTGGTAGCTCTGGGCGCAACGGTCATCTGTAAACAAGATCCCAGGCCTGGCTCCAGACAGCGGGCG
 ATCTGCCAGAGCCGGCCCCGACGCCATCATCGTCATAGGAGAAGGCTCACAAATGGGCCTGGACGAGTGTCAAGTTT
 CAGTTCCGCAATGGCCGCTGGAAGTGTCTGCACTGGGAGAGCGCACCGTCTTCGGGAAGGAGCTCAAAGTGGGG
 AGCCGGGACGGTGCCTTACCTACGCCATCATTGCCGCCGGCGTGGCCACGCCATCACAGCTGCCTGTACCCAT
 GGCAACCTGAGCGACTGTGGCTGCGACAAAGAGAAGCAAGGCCAGTACCACGGGACGAGGGCTGGAAGTGGGGT
 GGCTGCTCTGCCGACATCCGCTACGGCATCGGCTTCGCCAAGGTCTTCGTGGACGCTCGGGAGATCATGAAGAAC
 GCGCGGCGCCTCATGAACCTGCATAACAATGAGGCCGGCAGGAAGGTTCTAGAGGACCGGATGCAGCTGGAGTGC
 AAGTGCCACGGCGTGTCTGGCTCCTGCAACCAACAAACCTGTGGACCACGCTGCCCAAGTTCCGAGAGGTGGGC
 CACCTGCTGAAGGAGAAGTACAACGCGGCCGTGCAGGTGGAGGTGGTGCGGGCCAGCCGTCTGCGGCAGCCCACC
 TTCCTGCGCATCAAACAGCTGCGCAGCTATCGCAAGCCCATGAAGACGGACCTGGTGTACATCGAGAAGTCGCCC
 AACTACTGCGAGGAGGACCCGGTGACCGGCAGTGTGGGCACGCAGGGCCGCGCTGCAACAAGACGGCTCCCCAG
 GCCAGCGGCTGTGACCTCATGTGCTGTGGGCGTGGCTACAACACCCACCAGTACGCCCGCGTGTGGCAGTGCAAC
 TGTAAGTTCCACTGGTGTCTATGTCAAGTGCAACACGTGCAGCGAGCGCACGGAGATGTACACGTGCAAGTGA
GCCCCGTGTGCACACCACCTCCCGCTGCAAGTCAGATTGCTGGGAGGACTGGACCGTTTCCAAGCTGCGGGCTC
CCTGGCAGGATGCTGAGCTTGTCTTTCTGCTGAGGAGGGTACTTTTCTGGGTTTCTGTCAGGCATCCGTGGGG
GAAAAAATCTCTCAGAGCCCTCAACTATTCTGTTCCACACCCAATGCTGCTCCACCCTCCCCCAGACACAGCC
CAGGTCCCTCCGCGGCTGGAGCGAAGCCTTCTGCAGCAGGAACCTCTGGACCCCTGGGCCTCATCACAGCAATATT
TAACAATTTATTCTGATAAAAAATAATTTAATTTATTTAATTAAGAAATTCTTCCACCTCGTCGGGATCCGTT
TTCTGCAATCAAAGTGGACTGCTTGTCTTCTAGCAGGATGATTTTGTGCTAGGACAAGGAGCCGTGTAGAAGT
GTACATAACTATTCTTTATGCAGATATTTCTACTAGCTGATTTTGCAGGTACCCACCTTGCAGCACTAGATGTTT
AAGTACAAGAGGAGACATCTTTTATGCATATATAGATATACACACGAAAAA

The sequence of NOV5a was derived by laboratory cloning of cDNA fragments covering the full length and/or part of the DNA sequence of the invention, and/or by *in silico* prediction of the full length and/or part of the DNA sequence of the invention from public human sequence
 10 databases.

The DNA sequence and protein sequence for a novel Wnt-7a-like gene were obtained by SeqCalling™ Technology and are reported here as NOV5a. These methods used to amplify NOV5a cDNA are described in Example 2.

The NOV5a polypeptide (SEQ ID NO:16) encoded by SEQ ID NO:15 is 349 amino acid
 15 residues in length and is presented using the one-letter amino acid code in Table 5B. The SignalP, Psort and/or Hydropathy results predict that NOV5a has a signal peptide and is likely to be localized extracellularly with a certainty of 0.8200. In alternative embodiments, a NOV5a polypeptide is located to the lysosome (lumen) with a certainty of 0.1900, the endoplasmic

reticulum (membrane) with a certainty of 0.1000, or the endoplasmic reticulum (lumen) with a certainty of 0.1000.

Table 5B. Encoded NOV5a Protein Sequence (SEQ ID NO:16)

MNRKARRCLGHLFLSLGMVCLLACGFSSVVALGATVICNKIPGLAPRQRAICQSRPDIIIVIGEGSQMGLDECQ
FQFRNGRWNCALGERTVFGKELKVGSRDGAFTYAI AAGVAHAITAACHTGNLSDCGCDKEKQGYHRDEGWK
WGGCSADIRYGIGFAKVFVDAREIMKNARRLMNLHNEAGRKVL EDRMQLECKCHGVSGSCTTKTCWTTLPKFR
EVGHLLKEKYNAAVQVEVVRASRLRQPTFLRIKQLRSYRKPMKTDLVYIEKSPNYCEEDPVTGSGVTQGRACNK
TAPQASGCDLMCCGRGYNTHQYARVWQCNCXFWCCYVKCNTCSERTEMYTCK

NOV5b

In alternative embodiments, a NOV5 variant is NOV5b (alternatively referred to herein as 169475673), which includes a 966 nucleotide sequence (SEQ ID NO:17) shown in Table 5C below.

Table 5C. NOV5b Nucleotide Sequence (SEQ ID NO:17)

AGATCTCTGGGCGCAACGGTCATCTGTAAACAAGATCCCAGGCCTGGCTCCCAGACAGCGGGCGATCTGCCAGAG
CCGGCCCCGACGCCATCATCGTCATAGGAGAAGGCTCACAAATGGGCCCTGGACGAGTGTCAAGTTTCAGTTCCGCA
ATGGCCGCTGGAAGTCTGCTGCACTGGGAGAGCGCACCGTCTTCGGGAAGGAGCTCAAAGTGGGGAGCCGGGAG
GCTGCGTTACCTACGCCATCATTTGCCGCCGGCGTGGCCCCACGCCATCACAGCTGCCTGTACCCAGGGCAACCT
GAGCGACTGTGGCTGCGACAAAGAGAAGCAAGGCCAGTACCACCGGGACGAGGGCTGGAAGTGGGGTGGCTGCT
CTGCCGACATCCGCTACGGCATCGGCTTCGCCAAGGTCTTTGTGGATGCCCGGGAGATCAAGCAGAATGCCCGG
ACTCTCATGAACCTTGACACAACGAGGCAGGCCGAAAGATCCTGGAGGAGAACATGAAGCTGGAATGTAAGTG
CCACGGCGTGTCAAGGCTCGTGCACCACCAAGACGTGTGGACCACACTGCCACAGTTTCGGGAGCTGGGCTACG
TGCTCAAGGACAAGTACAACGAGGCCGTTTACGTGGAGCCTGTGCGTGCCAGCCGCAACAAGCGGCCACCTTC
CTGAAGATCAAGAAGCCACTGTCTACCGCAAGCCCATGGACACGGACCTGGTGTACATCGAGAAGTCGCCCAA
CTACTGCGAGGAGGACCCGGTGACCGGCAGTGTGGGCACCCAGGGCCGCGCTGCAACAAGACGGCTCCCCAGG
CCAGCGGCTGTGACCTCATGTGCTGTGGGCGTGGCTACAACACCCACAGTACGCCCCGCTGTGGCAGTGCAAC
TGTAAGTTCCACTGGTGCTGTATGTCAAGTGCAACACGTGCAGCGAGCGCACGGAGATGTACACGTGCAAGCT
CGAG

NOV5b is an insert assembly whose sequence was derived by laboratory cloning of cDNA fragments coding for a domain of the full length form of NOV5a (CG50353-01), between residues 32 to 349. The cDNA coding for the NOV5b sequence was cloned by the polymerase chain reaction (PCR). The PCR template is the previously identified plasma (NOV5a) when available or human cDNA. These primers and methods used to amplify NOV5b cDNA are described in Example 2.

The NOV5b polypeptide (SEQ ID NO:18) encoded by SEQ ID NO:17 is 322 amino acid residues in length and is presented using the one-letter amino acid code in Table 5D.

Table 5D. Encoded NOV5b Protein Sequence (SEQ ID NO:18)

RSLGATVICNKIPGLAPRQRAICQSRPDAIIVIGEGSQMGLDECQFQFRNGRWNCALGERTVFGKELKVGSR
AFTYAIIAAGVAHAITAACQGNLSDCGCDKEKQGQYHRDEGWKGWGGCSADIRYGIGFAKFVVDAREIKQNARTL
MNLHNNNEAGRKILEENMKLECKCHGVSGSCTTKTCWTTLPQFRELGYVLKDKYNEAVHVEPVRASRNKRPTFLKI
KKPLSYRKPMDDTLVYIEKSPNYCEEDPVTGSGVTQGRACNKTAPQASGCDLMCCGRGYNTHQYARVWQCNCCKFH
WCCYVKCNTCSERTEMYTCKLE

5 SNP variants of NOV5 are disclosed in Example 3.

NOV5 Clones

Unless specifically addressed as NOV5a or NOV5b, any reference to NOV5 is assumed to encompass all variants.

10 The amino acid sequence of NOV5 has high homology to other proteins as shown in Table 5E.

Table 5E. BLASTX Results from Patp Database for NOV5

Sequences Producing High-Scoring Segment Pairs:		High Score	Smallest Sum Prob P (N)
patp:AAB19789	Human Wnt-7a protein involved in kidney tubulogenesis	1784	1.1e-183
patp:AAY70737	Human Wnt-7a protein	1784	1.1e-183
patp:AAY57598	Human Wnt-7a protein	1784	1.1e-183
patp:AAY93965	Amino acid sequence of a human WNT-7A polypeptide	1758	6.1e-181
patp:AAR75881	Human Wnt-x	887	1.2e-88

15 In a search of sequence databases, it was found, for example, that the NOV5a nucleic acid sequence has 1336 of 1412 bases (94%) identical to a gb:GENBANK-ID:HSU53476|acc:U53476.1 mRNA from Homo sapiens (Human proto-oncogene Wnt7a mRNA, complete cds). Further, the full amino acid sequence of the disclosed NOV5a protein of the invention has 321 of 349 amino acid residues (91%) identical to, and 335 of 349 amino acid residues (95%) similar to, the 349 amino acid residue ptr:SWISSPROT-ACC:O00755 protein
20 from Homo sapiens (Human) (WNT-7A PROTEIN PRECURSOR).

Additional BLASTP results are shown in Table 5F.

Table 5F. NOV5 BLASTP Results

Gene Index/ Identifier	Protein/Organism	Length of aa	Identity (%)	Positives (%)	Expect Value
O00755	WNT-7A protein precursor - Homo sapiens (Human)	349	321/349 (91%)	335/349 (95%)	1.4e-183
AAH08811	UNKNOWN (PROTEIN FOR MGC:10346) - Homo sapiens (Human)	349	317/349 (90%)	333/349 (95%)	7.8e-181
Q9DBY3	WINGLESS-RELATED MMTV INTEGRATION SITE 7A - Mus musculus (Mouse)	349	315/349 (90%)	332/349 (95%)	8.9e-180
P24383	WNT-7A protein precursor - Mus musculus (Mouse)	349	313/349 (89%)	330/349 (94%)	3.5e-178
Q9DEB8	WNT-7A - Gallus gallus (Chicken)	349	302/349 (86%)	329/349 (94%)	4.7e-174

A multiple sequence alignment is given in Table 5G in a ClustalW analysis comparing NOV5 with related protein sequences disclosed in Table 5F.

Table 5G. ClustalW Analysis of NOV5

1. SEQ ID NO.: 16	NOV5a	5. SEQ ID NO.: 68	Q9DBY3
2. SEQ ID NO.: 18	NOV5b	6. SEQ ID NO.: 69	P24383
3. SEQ ID NO.: 66	O00755	7. SEQ ID NO.: 70	Q9DEB8
4. SEQ ID NO.: 67	AAH08811		

15	NOV5a	MNRKARRCLGHLFSLSLGMVCLLACGFSSVVALGATV	ICNKIPGLAPRQRAICQSRPDATII	60
	NOV5b	-----RSLGATV	ICNKIPGLAPRQRAICQSRPDATII	31
	O00755	MNRKALRCLGHLFSLSLGMVCLRIGGFSSVVALGATII	ICNKIPGLAPRQRAICQSRPDATII	60
	AAH08811	MNRKARRCLGHLFSLSLGMVYLRIIGGFSSVVALGASII	ICNKIPGLAPRQRAICQSRPDATII	60
	Q9DBY3	MTRKARRCLGHLFSLSLGIVYLRIIGGFSSVVALGASII	ICNKIPGLAPRQRAICQSRPDATII	60
20	P24383	MTRKARRCLGHLFSLSLGIVYLRIIGGFSSVVALGASII	ICNKIPGLAPRQRAICQSRPDATII	60
	Q9DEB8	MNRKTRRWLIFHLFSLSLGIVYIKIGGFSSVVALGASII	ICNKIPGLAPRQRAICQSRPDATII	60
25	NOV5a	VIGEGSQMGLDECQFQFRNGRWNCALGERTVFGKELKVGSRDCAFTYAIIAAGVAHAIT		120
	NOV5b	VIGEGSQMGLDECQFQFRNGRWNCALGERTVFGKELKVGSRDCAFTYAIIAAGVAHAIT		91
	O00755	VIGEGSQMGLDECQFQFRNGRWNCALGERTVFGKELKVGSRDCAFTYAIIAAGVAHAIT		120
	AAH08811	VIGEGSQMGLDECQFQFRNGRWNCALGERTVFGKELKVGSRDCAFTYAIIAAGVAHAIT		120
	Q9DBY3	VIGEGSQMGLDECQFQFRNGRWNCALGERTVFGKELKVGSRDCAFTYAIIAAGVAHAIT		120
	P24383	VIGEGSQMGLDECQFQFRNGRWNCALGERTVFGKELKVGSRDCAFTYAIIAAGVAHAIT		120
30	Q9DEB8	VIGEGSQMGLDECQFQFRNGRWNCALGERTVFGKELKVGSRDCAFTYAIIAAGVAHAIT		120
	NOV5a	AACTHGNLSDCGCDKEKQGOYHRDEGWKGGCSADIRYGIGFAKVFVDAREIMKNARRLM		180
	NOV5b	AACTQGNLSDCGCDKEKQGOYHRDEGWKGGCSADIRYGIGFAKVFVDAREIKQNARTLM		151

5	O00755	AACTHG N LSDCGCDKEKQGGVYHRDEGWKGGCSADIRYGIGFAKVFDAREIKQ N ARTLM	180
	AAH08811	AACTQGNLSDCGCDKEKQGGVYHRDEGWKGGCSADIRYGIGFAKVFDAREIKQ N ARTLM	180
	Q9DBY3	AACTQGNLSDCGCDKEKQGGVYHRDEGWKGGCSADIRYGIGFAKVFDAREIKQ N ARTLM	180
	P24383	AACTQGNLSDCGCDKEKQGGVYHRDEGWKGGCSADIRYGIGFAKVFDAREIKQ N ARTLM	180
	Q9DEB8	AACTQGNLSDCGCDKEKQGGVYHRDEGWKGGCSADIRYGIGFAKVFDAREIKQ N ARTLM	180
10	NOV5a	NLHNNEAGRKIVLEDRM Q LECKCHGVSGSCTTKTCWTTLPK F REVG H LLKEKYNAAVQ V EV	240
	NOV5b	NLHNNEAGRKILEENMKLECKCHGVSGSCTTKTCWTTLPQFRELGYVLKDKYNEAVHVEP	211
	O00755	NLHNNEAGRKILEENMKLECKCHGVSGSCTTKTCWTTLPQFRELGYVLKDKYNEAVHVEP	240
	AAH08811	NLHNNEAGRKILEENMKLECKCHGVSGSCTTKTCWTTLPQFRELGYVLKDKYNEAVHVEP	240
	Q9DBY3	NLHNNEAGRKILEENMKLECKCHGVSGSCTTKTCWTTLPQFRELGYVLKDKYNEAVHVEP	240
	P24383	NLHNNEAGRKILEENMKLECKCHGVSGSCTTKTCWTTLPQFRELGYVLKDKYNEAVHVEP	240
	Q9DEB8	NLHNNEAGRKILEENMKLECKCHGVSGSCTTKTCWTTLPK F RELGY L LKDKYNEAVQ V EV	240
20	NOV5a	VRASRLR Q PTFLRIK Q LRSYRKPM T DLVYIEKSPNYCEEDPVTGSGVTQGRACNKTAPO	300
	NOV5b	VRASRNKRPTFLKIKKPLSYRKPM T DLVYIEKSPNYCEEDPVTGSGVTQGRACNKTAPO	271
	O00755	VRASRNKRPTFLKIKKPLSYRKPM T DLVYIEKSPNYCEEDPVTGSGVTQGRACNKTAPO	300
	AAH08811	VRASRNKRPTFLKIKKPLSYRKPM T DLVYIEKSPNYCEEDPVTGSGVTQGRACNKTAPO	300
	Q9DBY3	VRASRNKRPTFLKIKKPLSYRKPM T DLVYIEKSPNYCEEDPVTGSGVTQGRACNKTAPO	300
	P24383	VRASRNKRPTFLKIKKPLSYRKPM T DLVYIE L SPNYCEEDPVTGSGVTQGRACNKTAPO	300
	Q9DEB8	VRASRNKRPTFLKIKKPLSYRKPM T DLVYIEKSPNYCEEDPVTGSGVTQGRM C NKTA Q Q	300
25	NOV5a	ASGCDLMCCGRGYNTHQYARVWQCNC K FHWCCYVKCNTCSERTE M YTCK--	349
	NOV5b	ASGCDLMCCGRGYNTHQYARVWQCNC K FHWCCYVKCNTCSERTE M YTCKLE	322
	O00755	ASGCDLMCCGRGYNTHQYARVWQCNC K FHWCCYVKCNTCSERTE M YTCK--	349
	AAH08811	ASGCDLMCCGRGYNTHQYARVWQCNC K FHWCCYVKCNTCSERTE M YTCK--	349
	Q9DBY3	ASGCDLMCCGRGYNTHQYARVWQCNC K FHWCCYVKCNTCSERTE M YTCK--	349
	P24383	ASGCDLMCCGRGYNTHQYARVWQCNC K FHWCCYVKCNTCSERTE M YTCK--	349
	Q9DEB8	SNGCDLMCCGRGYNTHQY S RVWQCNC K FHWCCYVKCNTCSERTE M YTCK--	349
30			

Domain results for NOV5 were collected from BLAST sample domains found in the Smart and Pfam collections, and then identified by the Interpro domain accession number. The results are listed in Table 5H with the statistics and domain description. These results indicate that the NOV5 polypeptides have properties similar to those of other proteins known to contain these domains and similar to the properties of these domains.

Table 5H. Domain Analysis of NOV5

PSSMs Producing Significant Alignments	Score (bits)	E Value
wnt: domain 1 of 1, from 37 to 349	716.5	3e-260

Wnt	lCrslPGLsprQrqlCrrnpdvmasvseGaglaigECQhQFRgrRWN
NOV5a	+ +++ +++ +++ ++++ ++++ ++++ +++ +++ +++ +++
	ICNKIPGLAPRQRAICQSRPDAIIVIGEGSQMGLDECQFQFRNGRWN
	CStldslnersvfgkvlkkgtrEtAFVyAIsSAGVahaVTRaCseGeles
NOV5a	+++ ++++ ++++ ++++ ++++ ++++ ++++ ++++ ++++
	CSALG---ERTVFGKELKVGSRDGAFTYAIIAAGVAHAITAACHTGNLSD
	CGCDdkRkadeerlrikLepkgpggpggsWkWGGSNDNvefGirfSReFV
NOV5a	+ ++++ +++ ++++ ++++ ++++ ++++ ++++ ++++
	CGCDK-----EKQGQYHRDEGKWGGCSADIRYGIGFAKVFV
	DarEreklmtksrdrdaRsLMNLHNNNEAGRkaVksmrrreCKCHGvSGSC
NOV5a	++ + ++ + + + + + + + + + + + + + + + + + + +
	DAREIM-----KN--ARRLMNLHNNNEAGRKVLEDRMQLECKCHGvSGSC
	slKTCWlsLPdFReVGdlLKeKYdgAieVevnkrkgqgrslssrkqasal
NOV5a	++ +
	TTKTCWTTLPKFREVGHLLKEKYNAAVQVEVVRASR-----LRQPTFLR
	eaanerfkkPtrnQYTDLVYlEkSPDYCerdretGslGTqGRvCnktSkG
NOV5a	+++ ++++ +++ + + + + + + + + + + + + + + + +
	IKQLRSYRKPMKT---DLVYIEKSPNYCEEDPVTGSGVTQGRACNKTAPO
	lgWRDgCellCCGRGYnteqKverttekCnCKFHNGWCCyVkCeeCteve
NOV5a	+ ++ +++ + + + + + + + + + + + + + + + + + +
	A---SGCDLMCCGRGYNTHQ-YARVWQCNCCKFH--WCCYVKCNTCSERTE
	vhtCK (SEQ ID NO:71)
NOV5a	+++
	MYTCK (SEQ ID NO:16)

The Wnt-7a-like protein disclosed in this invention is expressed in at least the following tissues: testis, pancreas, brain, coronary artery, dermis, prostate, uterus and ovary. This information was derived by determining the tissue sources of the sequences that were included in the invention, including but not limited to, SeqCalling sources, PublicEST sources, RACE sources, and publicly available reference material from OMIM and Pubmed.

The protein similarity information, expression pattern, and map location for the Wnt-7a-like protein and nucleic acid disclosed herein suggest that this protein may have important structural and/or physiological functions characteristic of the Wnt family. Therefore, the NOV5 nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications and as a research tool. For example, the compositions of the present invention will have efficacy for treatment of patients suffering from: atherosclerosis, aneurysm, hypertension,

fibromuscular dysplasia, stroke, scleroderma, obesity, transplantation disorders, myocardial infarction, embolism, cardiovascular disorders, bypass surgery, endometriosis, infertility, polycystic ovary syndrome, Von Hippel-Lindau (VHL) syndrome, Alzheimer's disease, tuberous sclerosis, hypercalcaemia, Parkinson's disease, Huntington's disease, cerebral palsy, epilepsy, 5 Lesch-Nyhan syndrome, multiple sclerosis, ataxia-telangiectasia, leukodystrophies, behavioral disorders, addiction, anxiety, pain, neurodegeneration, cancer, psoriasis, actinic keratosis, acne, hair growth/loss, alopecia, pigmentation disorders, endocrine disorders, pancreatitis, diabetes and other diseases, disorders and conditions of the like.

The novel nucleic acid encoding the Wnt-7a-like protein of the invention, or fragments 10 thereof, are useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed. These materials are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" 15 section below. The disclosed NOV5 protein has multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, a contemplated NOV5 epitope is from about amino acids 40 to 50. In another embodiment, a contemplated NOV5 epitope is from about amino acids 52 to 57. In other specific embodiments, contemplated NOV5 epitopes are from about amino acids 57 to 60, 65 to 100, 125 to 150, 165 to 210, 210 to 230, 230 to 240, 240 to 295, 20 300 to 325, and 325 to 340.

NOV6

Another NOVX protein of the invention, referred to herein as NOV6, includes two novel apical endosomal glycoprotein (AEG)-like proteins. The disclosed proteins have been named 25 NOV6a and NOV6b.

After endocytosis from the plasma membrane, internalized receptors and ligands are delivered to endosomes. The endosomal compartment performs a variety of functions, including the sorting of internalized receptors and ligands, and newly synthesized lysosomal membrane proteins and hydrolases. In polarized epithelial cells, the apical endosomal compartment plays a 30 role in both apical to basolateral and basolateral to apical transepithelial transport.

The NOV6 proteins disclosed here are predicted to localize at the plasma membrane. Therefore, it is likely that these proteins are accessible to a diagnostic probe, and for the various therapeutic applications described herein.

At least the NOV6a protein of the invention maps to chromosome 9. This information was assigned using OMIM, the electronic northern bioinformatic tool implemented by CuraGen Corporation, public ESTs, public literature references and/or genomic clone homologies.

NOV6a

In one embodiment, a NOV6 variant is NOV6a (alternatively referred to herein as CG50221-01), which encodes a novel apical endosomal glycoprotein (AEG)-like protein and includes the 3731 nucleotide sequence (SEQ ID NO:19) shown in Table 6A. An open reading frame for the mature protein was identified beginning with an ATG codon at nucleotides 39-41 and ending with a TAG codon at nucleotides 3699-3701. Putative untranslated regions downstream from the termination codon and upstream from the initiation codon are underlined in Table 6A, and the start and stop codons are in bold letters.

Table 6A. NOV6a Nucleotide Sequence (SEQ ID NO:19)

GCACCTGTGTGGCCGCACTGCTCCCTCTGGCCCAACCATGCCTCTGTCCAGCCACCTGCTGCCCGCCTTGGTCCT
 GTTCCTGGCAGCAGGGTCCTCAGGCTGGGCCTGGGTCCCCAACCACTGCAGGAGCCCTGGCCAGGCCGTGTGCAAC
 TTCGTGTGTGACTGCAGGGACTGCTCAGATGAGGCCAGTGTGGTTACCACGGGGCCTCGCCACCCCTGGGCGCCC
 CCTTCGCCTGTGACTTCGAGCAGGACCCCTGCGGCTGGCGGGACATTAGTACCTCAGGCTACAGCTGGCTCCGAGA
 CAGGGCAGGGGCCGCACTGGAGGGTCCTGGGCCTCACTCAGACCACACACTGGGCACCGACTTGGGCTGGTACATG
 GCCGTTGGAACCCACCGAGGGAAAGAGGCATCCACCGCAGCCCTGCGCTCGCCAAACCTGCGAGAGGCAGCCTCCT
 CTTGCAAGCTGAGGCTCTGGTACCACGCGGCTCTGGAGATGTGGCTGAACTGCGGGTGGAGCTGACCCATGGCGC
 AGAGACCTGACCTGTGGCAGAGCACAGGGCCCTGGGGCCCTGGCTGGCAGGAGTTGGCAGTGACCACAGGCCGC
 ATCCGGGGTGACTTCGAGTGACCTTCTCTGCCACCCGAAATGCCACCCACAGGGGCGCTGTGGCTCTAGATGACC
 TAGAGTTCTGGGACTGTGGTCTGCCACCCCCAGGCCAACTGTCCCCGGGACACCACCTGCCAGAACAAGGT
 CTGCGTGGAGCCCCAGCAGCTGTGCGACGGGGAAGACAAGTGGGGGACCTGTCTGATGAGAACCACTCACCTGT
 GGCCGCCACATAGCCACCGACTTTGAGACAGGCCTGGGCCCATGGAACCGCTCGGAAGGCTGGTCCCGGAACCAAC
 GCGCTGGTGGTCTGAGCGCCCCCTCTGGCCACGCCGTGACCACAGCCGGAACAGTGACAGGGCTCCTTCCTGGT
 CTCGTGGCCGAGCCTGGCACCCCTGCTATACTCTCCAGCCCCGAATTCCAAGCCTCAGGCACCTCCAAGTCTCG
 GTGAGATGGCTGGTCTTCTATCAGTACCTGAGTGGGTCTGAGGCTGGCTGCCTCCAGCTGTTCTGCAGACTCTGG
 GGCCCGCGCCCCCGGGCCCCCGTCTGTGCGGAGGCGCCGAGGGGAGCTGGGGACCGCTGGGTCCGAGACCG
 TGTGACATCCAGAGCGCTACCCCTTCAGATCCTCTGGCCGGGCAGACAGGCCCGGGGGCGTCTGTGGTCTG
 GACGACCTCATCTGTCTGACCACTGCAGACAGTCTCGGAGGTGTCCACCCTGCAGCCGCTGCCTCCTGGGCCCC
 GGGCCCCAGCCCCCAGCCCCGCGCCAGCTCGCGGCTCCAGGATTCCTGCAAGCAGGGGCATCTTGCCTGCGG
 GGACCTGTGTGTGCCCCCGGAACAAGTGTGTGACTTCGAGGAGCAGTGCGCAGGGGGCGAGGACGAGCAGGCCTGT
 GGCACCACAGACTTTGAGTCCCCGAGGCTGGGGCTGGGAGGACGCCAGCGTGGGGCGGCTGCAGTGGCGGCGTG
 TCTCAGCCCAGGAGAGCCAGGGTCCAGTGACGCTGCTGGGCACTTCTGTCTCTGCAGCGGGCTGGGGGCA
 GCTAGGCGCTGAGGCCCGGGTCCCTCACACCCCTCCTTGGCCCTTCTGGCCCCAGCTGTGAACTCCACCTGGCTTAT
 TATTTACAGAGCCAGCCCCGAGGCTTCTGGCACTAGTTGTGGTGGACAACGGCTCCCGGGAGCTGGCATGGCAGG
 CCTGAGCAGCAGTGCAAGCATCTGGAAGGTGGACAAGGTCTTCTAGGGGCCCGCCGCGCCCTTCCGGCTGGA

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GTTTGTGCGTTTGGTGGACTTGGATGGCCCTGACCAGCAGGGAGCTGGGGTGGACAACGTGACCCTGAGGGACTGT
AGCCCCACAGTGACCACCGAGAGAGACAGAGAGGTCTCCTGTAACCTTTGAGCGGGACACATGCAGCTGGTACCCAG
GCCACCTCTCAGACACACACTGGCGCTGGGTGGAGAGCCGCGGCCCTGACCACGACCACACCACAGGCCAAGGCCA
CTTTGTGCTCCTGGACCCACAGACCCCTGGCCTGGGGCCACAGTGCCACCTGCTCTCCAGGCCCCAGGTGCCA
GCAGCACCCACGGAGTGTCTCAGCTTCTGGTACCACCTCCATGGGCCCCAGATTGGGACTCTGCGCCTAGCCATGA
GACGGGAAGGGGAGGAGACACACCTGTGGTTCGCGGTTCAGGCACCCAGGGCAACCGCTGGCAGGAGGCTGGGGCCAC
CCTTTCCACCAGCCTGGCTCCCATGCCCAGTACCAGCTGCTGTTTCGAGGGCCTCCGGGACGGATAACCACGGCACC
ATGGCGCTGGACGATGTGGCCGTGCGGCCGGGCCCCCTGCTGGGCCCCCTAATTACTGCTCCTTTGAGGACTCAGACT
GCGGCTTCTCCCCTGGAGGCCAAGGTCTCTGGAGGCGGCAGGCCAATGCCTCGGGCCATGCTGCCTGGGGCCCCC
AACAGACCATAACCACTGAGACAGCCCCAAGGGCACTACATGGTGGTGGACACAAGCCCAGACGCACTACCCCGGGGC
CAGACGGCCTCCCTGACCTCCAAGGAGCACAGGCCCTGGCCCAGCCTGCTTGTCTGACCTTCTGGTACCACGGGA
GCCTCCGCAGCCAGGCACCCCTGCGGGTCTACCTGGAGGAGCGCGGGAGGCACCAGGTGCTCAGCCTCAGTGCCCA
CGGCGGGCTTGCCTGGCGCCTGGGCAGCATGGACGTGCAGGCCGAGCGAGCCTGGAGGGTGGTGT'TTGAGGCAGTG
GCCGCAGGCGTGGCACACTCCTACGTGGCTCTGGATGATCTGCTCCTCCAGGACGGGCCCTGCCCTCAGCCAGGTT
CCTGTGATTTTGAAGTCTGGCCTGTGTGGCTGGAGCCACCTGGCCTGGCCCCGGCCTGGGCGGATACAGCTGGGACTG
GGGCGGGGGAGCCACCCCTCTCGTTACCCCCAGCCCCCTGTGGACCACACCCTGGGCACAGAGGCAGGCCACTTT
GCCTTCTTTGAACTGGCGTGCTGGGCCCCGGGGGCCGGGCCGCTGGCTGCGCAGCGAGCCTCTGCCGGCCACCC
CAGCCTCCTGCCTCCGCTTCTGGTACCACATGGGTTTCTCTGAGCACTTCTACAAGGGGGAGCTGAAGGTACTGCT
GCACAGTGCTCAGGGCCAGCTGGCTGTGTGGGGCGCAGGCGGGCATCGGCGGCACCAAGTGGCTGGAGGCCCAGGTG
GAGGTAGCCAGTGCCAAGGAGTTCAGATCGTGT'TTGAAGCCACTCTGGGCGGCCAGCCAGCCCTGGGGCCCCATTG
CCCTGGATGACGTGGAGTATCTGGCTGGGCAGCATTGCCAGCAGCCTGCCCCAGCCCCGGGGAAACAGCCGCACC
CGGTCTGTGCCAGCTGTGGTTGGCAGTGCCCTCCTATTGCTCATGCTCCTGGTGCTGCTGGGACTTGGGGGACGG
CGCTGGCTGCAGAAGAAGGGGAGCTGCCCCCTTCCAGAGCAACACAGAGGCCACAGCCCCCTGGCTTTTGACAACATCC
TTTTCAATGCGGATGGTGTACCCCTCCCGGCATCTGTACACAGTGATCCGTAGACCACCCAGACAAGGCC
CGCTTCCTCAC

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The sequence of NOV6a was derived by laboratory cloning of cDNA fragments, by *in silico* prediction of the sequence. The cDNA fragments covering either the full length of the DNA sequence, or part of the sequence, or both, were cloned. *In silico* prediction was based on sequences available in CuraGen's proprietary sequence databases or in the public human sequence databases, and provided either the full length DNA sequence, or some portion thereof.

The NOV6a polypeptide (SEQ ID NO:20) encoded by SEQ ID NO:19 is 1220 amino acid residues in length and is presented using the one-letter amino acid code in Table 6B. The SignalP, Psort and/or Hydropathy results predict that NOV6a has a signal peptide and is likely to be localized extracellularly at the plasma membrane with a certainty of 0.4600. In alternative embodiments, a NOV6a polypeptide is located to the microbody (peroxisome) with a certainty of 0.2742, the endoplasmic reticulum (membrane) with a certainty of 0.1000, or the endoplasmic reticulum (lumen) with a certainty of 0.1000. The SignalP predicts a likely cleavage site for a NOV6a peptide between amino acid positions 23 and 24, i.e. at the dash in the sequence GWA-
WV.

Table 6B. Encoded NOV6a Protein Sequence (SEQ ID NO:20)

MPLSSHLLPALVLFLLAAGSSGWAVPNHCRSPGQAVCNFVCDRCDSDEAQCGYHGASPTLGAPFACDFEQDPC
 GWRDISTSQYSWLRDRAGAALGPGPHSDHTLGTDLGWYMAVGTHRGKEASTAALRSPTLREAASSCKLRLWYH
 AASGDVAELRVELTHGAETLTWQSTGPGWGPWQELAVTTGRIRGDFRVTFSSATRNATHRGAVALLDDLEFWDCG
 LPTPQANCPPGHHHCQNKVCVEPQQLCDGEDNCGDLSDENPLTCGRHIATDFETGLGPWNRSEGWSRNRHAGGP
 ERPSWPRRDHSRNSAQGSFLVSVAEPGTPAILSSPEFQASGTSNCSVRWLVFYQYLSGSEAGCLQLFLQTLGPG
 APRAPVLLRRRRGELGTAWVRDRVDIQSAYPFQILLAGQTGPGGVVGLDDLILSDHCRPVSEVSTLQPLPPGPR
 APAPQPLPPSSRLQDSCQGHLAGDLCVPPEQLCDFEEQCAGGEDEQACGTTDFESPEAGGWEDASVGRQLQWR
 RVSAQESQGSAAAAGHFLSLQRAWGQLGAEARVLTPLLGPSPGSCLEHLLAYYLSQPRGFLALVVVDNGSREL
 AWQALSSSAGIWKVDKVLGARRRPFRLFVGLVDLDGPDQAGVDNVTLRDCSPTVTTERDREVS CNFERDT
 CSWYPGHLSDTHWRWVESRGPDDHTTGQGHFVLLDPTDPLAWGHSALLSRPQVPAAPTECLSFYHLLHGPQI
 GTLRLAMRREGEETHLWSRSGTQGNRWHEAWATLSHQPQSGHAQYQLLFEGLRDGYHGTALDDVAVRPGPCWAP
 NYCSFEDSDCGFSPGGQGLWRRQANASGHAAGPPTDHTTETAQGHYMVVDTPDALPRGQTASLTSKEHRPLA
 QPACLTFWYHGSRLSPGTLRVYLEERGRHQVLSLSAHGGLAWRLGSMVDQAERAWRVFEAVAAGVAHSYVALD
 DLLLQDGPQPGSCDFESGLCGWSHLAWPGLGGYSWDWGGGATPSRYPQPPVDHTLGTGTEAGHFAFFETGVLGP
 GGRAAWLRSEPLPATPASCLRFWYHMGFPHEFYKGLKVLHLSAQGQLAVWGAGGHRHQWLEAQVEVASAKEF
 QIVFEATLGGQPALGPALDDVEYLAGQHCQQPAPSPGNTAAPGSVPAVVGSALELLMLLVLLGLGGRRLQKK
 GSCPFQSNTEATAPGFDNLFNADGVTLPASVTS DP

NOV6b

In an alternative embodiment, a NOV6 variant is NOV6b (alternatively referred to herein
 as 174308633), which includes 1857 nucleotides. NOV6b is an insert assembly that was found to
 encode an open reading frame between residues 31 and 648 of the target sequence of NOV6a.
 NOV6b differs from NOV6a at 4 nucleotide and 4 amino acid positions. It also contains a 3
 amino acid deletion, and a 9 nucleotide deletion in comparison with NOV6a. Table 6C notes the
 changes in nucleotide and amino acid sequences from the parent clone, NOV6a.

Table 6C.

Nov No.	Alternate Reference	Change in DNA Seq. from NOV6a	Change in Protein Seq. from NOV6a
6b	174308633	T → C at bp 385; C → T at bp 914; C → T at bp 1007; and G → A at bp 1014	V → A at aa 116; A → T at aa 326; T → L at aa 649; and V → E at aa 650

The sequence of NOV6b was derived by laboratory cloning of cDNA fragments coding
 for a domain of the full length form of NOV6a, between residues 31 and 648. The cDNA coding
 for the NOV6b sequence was cloned by the polymerase chain reaction (PCR). The PCR template
 is the previously identified plasma (NOV6a) when available or human cDNA. These primers and
 methods used to amplify NOV6b cDNA are described in Example 2.

SNP variants of NOV6 are disclosed in Example 3.

NOV6 Clones

Unless specifically addressed as NOV6a or NOV6b, any reference to NOV6 is assumed to encompass all variants.

The amino acid sequence of NOV6 has high homolgy to other proteins as shown in Table 6D.

Table 6D. BLASTX Results from Patp Database for NOV6

Sequences Producing High-Scoring Segment Pairs:		High Score	Smallest Sum Prob P (N)
patp:AAB42780	Human ORFX ORF2544 polypeptide	1274	2.5e-230
patp:AAB01432	Human TANGO 239 (form 2)	377	2.4e-33
patp:AAB00036	Human TANGO 239 partial sequence	281	4.9e-21
patp:AAB01426	Human TANGO 239	271	2.5e-19
patp:AAE00585	Human nuclear cell adhesion molecule homologue	225	2.3e-14

In a search of sequence databases, it was found, for example, that the NOV6a nucleic acid sequence of this invention has 913 of 945 bases (96%) identical to a gb:GENBANK-ID:HSM801957|acc:AL137659.1 mRNA from Homo sapiens (Homo sapiens mRNA; cDNA DKFZp434I1716 (from clone DKFZp434I1716)). Further, the full amino acid sequence of the disclosed protein of the invention has 885 of 1220 amino acid residues (72%) identical to, and 990 of 1220 amino acid residues (81%) similar to, the 1216 amino acid residue ptrn:SWISSPROT-ACC:Q63191 protein from Rattus norvegicus (Rat) (APICAL ENDOSOMAL GLYCOPROTEIN PRECURSOR).

Additional BLASTP results are shown in Table 6E.

Table 6E. NOV6 BLASTP Results

Gene Index/ Identifier	Protein/Organism	Length of aa	Identity (%)	Positives (%)	Expect Value
Q63191	Apical endosomal glycoprotein precursor - Rattus norvegicus (Rat)	1216	885/1220 (72%)	990/1220 (81%)	0.0
Q91641	Thyroid hormone-induced protein B precursor - Xenopus laevis (African clawed frog)	688	131/452 (28%)	212/452 (46%)	1.4e-31

O88799	Zonadhesin precursor - Mus musculus (Mouse)	5376	146/502 (29%)	228/502 (45%)	9.8e-28
Q99ND0	ZAN - Mus musculus (Mouse)	5374	146/502 (29%)	227/502 (45%)	1.3e-27
Q9BZ84	ZONADHESIN VARIANT 5 - Homo sapiens (Human)	2601	149/491 (30%)	215/491 (43%)	5.4e-23

A multiple sequence alignment is given in Table 6F, with the NOV6 protein of the invention being shown in lines 1 and 2, in a ClustalW analysis comparing NOV6 with related protein sequences of Table 6E.

Table 6F. ClustalW Analysis of NOV6

1. SEQ ID NO.: 20	NOV6a	4. SEQ ID NO.: 74	O88799
2. SEQ ID NO.: 72	Q63191	5. SEQ ID NO.: 75	Q99ND0
3. SEQ ID NO.: 73	Q91641	6. SEQ ID NO.: 76	Q9BZ84
NOV6a	MPLSSHLLPALVLFLLAAGSSGWAVPNHCRSPGQAVCNFVCDQDCSDEAOCGGYHGASPT	60	
Q63191	MCLPSCLESIFVLFMAAQSILGKTWVPDHCSPTEATCNFVCDQDCSDEAOCGGFHGASTT	60	
Q91641	-----MMLSHVLLLSLGAIVW-----LAE--GGEISPGSCTFEN-----	32	
O88799	-----MALPVWILMLLVGAAGQEQVPAWRPNSPDLGPMVHTSREDSILSKCDFE-----	50	
Q99ND0	-----MALPVWILMLLVGAAGQEQVPAWRPNSPDLGPMVHTSREDSILSKCDFE-----	50	
Q9BZ84	-----MVPPVWILMLLVGAALFRKEP-----PDQKLVVRSSRDNYVLTCDFE-----	44	
NOV6a	LGAPFACDFEODPCGWRDISTSQYSWLRDRAGAALGPGPHSDHTLGTDLGWYMAVGTHR	120	
Q63191	PNTPTFTCNFEODPCGWODISTSQYRWLRDRAGAGLDSSGPHSDHTRGTDLGWYMAVGTHS	120	
Q91641	-----STCAYTSAFP-FLOWTVN-----IEG-----HYVSVDSNS	61	
O88799	-----DNSRPFCQWSQSADDGDWIRTTGPSLTGTSGPPGGYPNGE--GYLHMDPKT	101	
Q99ND0	-----DNSRPFCQWSQSADDGDWIRTTGPSLTGTSGPPGGYPNGE--GYLHMDPKT	101	
Q9BZ84	-----DDAKPLCDWSQVSADDEDWVRASGPSPGTGSGTAPGGYPNGE--GSLHMEENS	95	
NOV6a	GKEASTAALRSEPTLREAASSCKLRLWYHAASGDVIELRVELTHG---AETLTWQSTGPW	177	
Q63191	GKEPSTRTLRSPVMREAAPTCELRLWYHTDSRDVIELRLDLTHG---METLTWQSSGPW	177	
Q91641	GLRGQKAVLISPDHLAEWSCLRLVYQIAGSESSPSSSLNVFVRPEGESFDYLLWSAEE	121	
O88799	FPQGGVARLRSPDIWEQGPLCVHFAFHMFGLSWGAOLRLILLRGRKHLRPYVLWKHVNTQ	161	
Q99ND0	FPQGGVARLRSPDIWEQGPLCVHFAFHMFGLSWGAOLRLILLRGRKHLRPYVLWKHVNTQ	161	
Q9BZ84	FHRGGVARLLSPDLWEQGPLCVHFAHMFGLSWGAOLRLILLSGEGRPDVILWKHVNTQ	155	
NOV6a	GEG-WQELAVTTGRIRGDFRVTFESATRNATHRGAVALLDMEFWD-----CGLPT	225	
Q63191	GEWPGRRELAVNTGRIQGDVKVTFESATRNATHRGAVALLDMEFWD-----CGLPI	226	
Q91641	HSDSWLISSIDLKNTTKRFKIIILEGVLGENTMSSIALFEVKMTTG-----YCIECDFEE	175	
O88799	SPSWMPTTVTVPADHDIPSWMFEFGMRGNTAYLDISLDGLSIQRGTCNQVCMSQMCTFDT	221	
Q99ND0	SPSWMPTTVTVPADHDIPSWMFEFGMRGNTAYLDISLDGLSIQRGTCNQVCMSQMCTFDT	221	
Q9BZ84	RPSWMLTTTVTPAGFTLPTRLMFEFGTRGSTAYLDIALDALSIIRGSCNRVCMQTCSDFI	215	
NOV6a	PQANCPPGHHHCQNKVCVEPQQLCDGEDNCGDLSDENPLTCCRHIATDFETG-----	277	
Q63191	PQARCPPLGHHHCQNKACVEPHQLCDGEDNCGDSSDEPLICSHHMTDFETG-----	278	
Q91641	N-HLCGYMNSWNPVNVFVGGGNVKNHSILPRDHTLNNELGHYMYVDSVYVK-----	227	
O88799	LNDLCGWSWVPTATGAKWTQKKGPTCKQGVCPAEDFSNPGNGYMLLDSTNARPGQKAVL	281	

	Q99ND0	LNDLQGSWSVPTATGAKWTQKKGPTGKQGVGPAEDFSNPGNCGYMLLDSTNARPGQKAVL	281
	Q9BZ84	PNDLQDWTWIPTASGAKWTQKKGSSCKPGVGPDCGDFSSPGSGCYMLLDPKNARPGQKAVL	275
5	NOV6a	LGPWNRSEGWS-----RNHRAGCSPERPSPRRDHSRN	309
	Q63191	LGPWTQLEGWT-----RNFSAGSMVSPAPHRDHSRN	310
	Q91641	-----HFOEVAQLVSP-----	238
	O88799	LSPLSHSRGCMTSLSFHYIMHGQGHEEGLFVYATFLGNIRKYTLFSCHPGPDWQAVSVNYT	341
	Q99ND0	LSPLSHSRGCMTSLSFHYIMHGQGHEEGLFVYATFLGNIRKYTLFSCHPGPDWQAVSVNYT	341
10	Q9BZ84	LSPVSLSSGCLSFHSFYILRGQSPGAALHIYASVLGSIRKHTLFSQCPGNWQAVSVNYT	335
	NOV6a	SAQGSFLVMSVAEPG-----TPAILSSPEHQASGTSNCSV-----	343
	Q63191	SAYGFFLVSVAKPG-----TTAVLYSPEHQGSVSYNCS-----	343
	Q91641	-----LIITPISG-----	246
15	O88799	GQGQIQFMVVGMMFGNIPEPAIAVDAISIAPCGESFPQCDHFEDRVHPFCDWNQVYGDGMHW	401
	Q99ND0	GQGQIQFMVVGMMFGNIPEPAIAVDAISIAPCGESFPQCDHFEDRVHPFCDWNQVYGDGMHW	401
	Q9BZ84	AVGRIQFAVVGVFCKTPEPAVAVDATSIAPCGEGFPQCDHFEDNAHPFCDWNQVTSGDGGHW	395
	NOV6a	-----RWLVFYQYLSGSEAG-----CLQLFLQ	365
20	Q63191	-----FTFYLYLHGSEAN-----QFQLFVQ	363
	Q91641	-----CLSEFYQLQRETSN-----IFLVH	265
	O88799	SWGSKSVPTLIAGSPREFPYGGEHYLFEDSVKLSQEGQSARLVSPPFCA PGGICVEFAYH	461
	Q99ND0	SWGSKSVPTLIAGSPREFPYGGEHYLFEDSVKLSQEGQSARLVSPPFCA PGDICVEFAYH	461
	Q9BZ84	ALGHKNGPVHGMGPAGGFNPAGGHYLYLEADEFSSQAGQSVRLVSRPFCA PGDICVEFAYH	455
25	NOV6a	TLGPG-----APRAPVLLRRRRGELGTAWVRDRVDIQS--AYPFQILLIAG---	408
	Q63191	AQGLN-----TTQPPVLLRSRHGELGTAWVRDRVDIQS--AHPFRILLIAG---	406
	Q91641	TRDLHG-----SYDEIWKMGAVRQGEWNLAEVDLNA--HVPLEVIFEV---	306
	O88799	MYGLGKGTTLKLLLGSPAGSSPIPLWNRVGSQSSGWMNSSVTIPKGYQQPMOLFIEATRG	521
	Q99ND0	MYGLGKGTTLKLLLGSPAGSFPPIPLWNRVGSQSSGWMNSSVTIPKGYQQPMOLFIEATRG	521
30	Q9BZ84	MYGLGEGTMLELLLGSPAGSPPPIPLWNRVGSQRPYQNTSVITVPSGHQQPMOLFIFKGIQG	515
	NOV6a	-----QTGPGGVVG-----	417
	Q63191	-----ETGPGGFVG-----	415
	Q91641	-----AFNG-----	310
35	O88799	TSTAFVVALNFILISHGPCRVLLQTEIPSSPLLPTGPESESTVPTLPMEQPTSPTKATTV	581
	Q99ND0	TSTAFVVALNFILISHGPCRVLLQTEIPSSPLLPTGPESESTVPTLPMEQPTSPTKATTV	581
	Q9BZ84	SNTASVVAMGFILINPGTCVPKVLPELPPVSPVSSSTGPESETTG---LTENPTISTKKPTV	572
	NOV6a	-----	417
40	Q63191	-----	415
	Q91641	-----	310
	O88799	TIEIPTTPTEEATIPTETTTVPTEVINVSPKETSIPPEVTIPTTEVITVSPEEIIISPTTEVT	641
	Q99ND0	TIEIPTTPTEEATIPTETTTVPTEVINVSPKETSIPPEVTIPTTEVITVSPEEIIISPTTEVT	641
45	Q9BZ84	SIEKPSVTTEKPTVPKEKPTIPTTEKP-----TISTEKPTIPSEKPNMPSEKP	619
	NOV6a	-----	417
	Q63191	-----	415
	Q91641	-----	310
50	O88799	PVPTDVTAAYVEATNASPEETSVPPEVTILTEVTTVSPEETTVPTTEVPIVLIEATAFPTG	701
	Q99ND0	PVPTDVTAAYVEATNASPEETSVPPEVTILTEVTTVSPEETTVPTTEVPIVLIEATAFPTG	701
	Q9BZ84	TIPSEKPTILTEKPTIPSEKPTIP-----SEKPTISTEKPTVPTEETTPTEETTSME	673
	NOV6a	-----	417
55	Q63191	-----	415
	Q91641	-----	310
	O88799	ETTLYTEVPTVPTEVTGVHTEVTNVSPETSVPTEETISTEVTTVSPEETTVPTTEVPIVL	761
	Q99ND0	ETTLYTEVPTVPTEVTGVHTEVTNVSPETSVPTEETISTEVTTVSPEETTVPTTEVPTVS	761

	Q9BZ84	EPVIPTEKPSIPTKPSIPTKPTISMEET-----IISTEKPTISPEKPTIPTKPTIP	727
	NOV6a	-----	
	Q63191	-----	417
5	Q91641	-----	415
	O88799	IEATASPTGEITLYTEVPTVPTEVTGVHTEVTVNSPEETSVPTEET-ISTEVTTVSPEET	310
	Q99ND0	TEVTVNSPEETSVPPEE-TILTEITTVSPEETVEPTEGTTLPTEVLTVPTEVTTFTGET	820
	Q9BZ84	TEKSTISPEKPTTPTEKPTIPTKPTISPEKPTTPTEKPTISPEKLTIPTEKPTIPTKPT	787
10	NOV6a	-----	
	Q63191	-----	417
	Q91641	-----	415
	O88799	TLPTVPTVSTEVTVNSPEETSVPPEETILTTLTEVP--TVPTVTVGVHTEVTVNSPEE	310
	Q99ND0	TVPTVPTVSTEMTGVHTEVTVTFPEETSIPTEVATVLPASIPPEETTTTTEVTTTPPEE	878
15	Q9BZ84	TIPTEKPTISTEEP-----TTPTEETTISTEKPSIPMEK	821
	NOV6a	-----	
	Q63191	-----	417
	Q91641	-----	415
20	O88799	TSVPTTEETISTEVTTVSPEETTLPTVPTVSTEVTVNSPEETSVPPEETILTTEITTVSPE	310
	Q99ND0	TTIPAEVTTVPVSIPS-EETTTTPEVTTTPPEETTIPAEVTTVPP-VSIPSEETTTTTE	938
	Q9BZ84	PTLPTEETTT-----SVEETTISTEKLTPMEKPTISTEKPTIP-----TEKPTISPE	869
	NOV6a	-----	
25	Q63191	-----	417
	Q91641	-----	415
	O88799	ETVFPPIEGTTLPTEVLTVPTEVTTFTGETTVPTVPTVSTEMTGVHTEVTVTFPEETS	310
	Q99ND0	VTTTPPEETTIPAEVTTVP--PVSIPSEETTIPTEVTTVPPEETTIPAEVTTVPPVSIPS	998
30	Q9BZ84	KLTIPTKLTIPTEKPTIPIEETTISTEKLTIPTKPTISPE-----	911
	NOV6a	-----L-----DDLILSDHCRPVS	
	Q63191	-----L-----DDLIMSNHCILVP	431
	Q91641	-----	429
	O88799	PTEVATVLPASIPPEETTTTPEVTTTPPEETTIPAEVTTVPPASIPPEETASLTEVTTTP	310
35	Q99ND0	EETTTIPTEVTTVPPEETTIPAEVTTTPPEETTIPTEVTTVPPASIPPEETASLTEVTTTP	1058
	Q9BZ84	----KP----TISTEKPTIPTKPTIPTTEETTISTEKLTIPT-----TEKPTIS	951
	NOV6a	-----EVSTLQPLP[PGPRAPAP	
40	Q63191	-----GMSTLQSSLG---PVP	448
	Q91641	-----	443
	O88799	PEETTTTPTEVTTVPPEKTTIPTTEVTTVPASIFPEETTVPPEETTIASEETTIVSTQETTL	310
	Q99ND0	PEETTTTPTEVTTVPPEKTTIPTTEVTTVPASIFPEETTVPPEETTIASEETTIVSTQETTL	1118
	Q9BZ84	PEKLTIPTEKPTISTEKPTIPTKLTIP---T-EKPTIPTKPTIPTKLTATA-----L	1116
45	NOV6a	-----QPLPSSRLQDS-----	1000
	Q63191	-----LALYQTSIKRT-----	460
	Q91641	-----	455
	O88799	LTEQSAVTQTSIACRPPCPSPPLMBIGPILSKPPGVSMFSLAPTTGVSTTESCPPNAHIE	310
50	Q99ND0	LTEQSAVTQTSIACRPPCPSPPLMBIGPILSKPPGVSMFSLAPTTGVSTTESCPPNAHIE	1178
	Q9BZ84	RPPHPSPTATGLAALVMSPHAPSTEMTSVILG---T-----T-TTSRSSTERCPPNARYE	1176
	NOV6a	-----CKQGHLAGCDLCPPE-----Q	1051
	Q63191	-----CDAGHLSCELCVPPE-----Q	477
	Q91641	-----IQAGYVALDDILFSPVS-----	472
55	O88799	LCACPASCESPKPSCQPPCIPGCVNPGFLFSNNOCINNESSCNCYPYNNKHYKPGEEWFTP	327
	Q99ND0	LCACPASCESPKPSCQPPCIPGCVNPGFLFSNNOCINNESSCNCYPYNNKYYKPGEEWFTP	1238
	Q9BZ84	SCACPASCKSPRPSGGLCREGCVNPGFLFSNDH[QIASSCNCFYNNDDYYEPGAEWFS	1236
			1111

5	NOV6a	LCDFEEQACAGGE---DEQACGTTDFESP EAGGWEDASVG-----	513
	Q63191	LCDFQOHCAGE---DEEKCGTTDFESASAGGWEDISIG-----	508
	Q91641	-----CSGQEGMFFDAREAG-CDFEEGMCQFHQDDNNG-----	359
	088799	NCTERCRCRLPGSLMECQISQCGTHTVCQLKSDQYQCEPYG-KATCLVYGD LHFVTFDERH	1297
	Q99ND0	NCTERCRCRLPGSLMECQISQCGTHTVCQLKSDQYQCEPYG-KATCLVYGD LHFVTFDERH	1295
	Q9BZ84	NCTEHCRCWPGRSRVECQISQCGTHTVCQLKNGQYGCHPYAGTATCLVYGD PHYVTFDGRH	1171
10	NOV6a	-----RLQWRVSAQES-----	525
	Q63191	-----KLOWQRAEAQESGK-----	522
	Q91641	-----SGWSRVKVKPN-----	370
	088799	IGFTGTCTYILTQTCSNSTDHFRTITANTEERGVEGVSCLDKVVISLPETTVMISGRHT	1357
	Q99ND0	IGFTGTCTYILTQTCSNSTDHFRTITANTEERGVEGVSCLDKVVISLPETTVMISGRHT	1355
15	Q9BZ84	FGFMGKCTYILAQPCGNSTDFEFRTAKNEEQQEGVSCLSKVYVTLPESTVTLLKGRRT	1231
20	NOV6a	-----QGSSAAAAGHFLSLQRAWGQ-----LGAEARVLTPLLGPS	560
	Q63191	-----PARDTNRNAPGHFLSLRKAWGQ-----LRSEARALTPTLGPS	559
	Q91641	-----AYQMGDHTTGLGVEMIANTRFTG-----QPAYFGRVYGPS	405
	088799	LIGDQEVTLPAILSDDTYVGLSGREVELRTTFGLRVRWDGDQQLFVTVSSTFSGKLCGFC	1417
	Q99ND0	LIGDQEVTLPAILSDDTYVGLSGREVELRTTFGLRVRWDGDQQLFVTVSSTFSGKLCGFC	1415
	Q9BZ84	LVGGQQVTLPAIPSKGVFLGASGREVELQTEFGLRVRWDGDQQLYVTVSSTYSGKLCCLC	1291
25	NOV6a	G-----PSCFLHL-----	568
	Q63191	G-----PHCELHM-----	567
	Q91641	LP-----G-----NIQYCIFFYS-	419
	088799	GNYDGDSSNDNLKSDGMMTHDEEELRLSWQVEEDEDKDWVSSRCQKKQNPSCDAALGST	1477
	Q99ND0	GNYDGDSSNDNLKSDGMMTHDEEELRLSWQVEEDEDKDWVSSRCQKKQNPSCDAALGST	1475
	Q9BZ84	GNYDGNSDNDHLKLDGSPAGDKEELGNSWQTDQDEDQ---ECQKYQVNSPSCDSSIQSS	1348
30	NOV6a	-----AYYLQSQPRGFLALVVDNGSRELAWQALSSSAGIWKVDKVL	610
	Q63191	-----TYFHHSHPOGFLALAVVENGFRLLWQAPSSSSGGWTLQKIL	609
	Q91641	-----LYGFYKTTIDSLAVYIFEENHVQEKIWSAHETPKGVWLQAEI	461
	088799	MSGPKLCGQLVNPSGPFACLIHLKASSELDNCVTDMCSEFOGLOQKLCARMSAMTATCQD	1537
	Q99ND0	MSGPKLCGQLVNPSGPFACLIHLKASSELDNCVTDMCSEFOGLOQKLCARMSAMTATCQD	1535
35	Q9BZ84	MSGPGFCGRLVDTHGPFETCLHVKAASEFDSCMLDMCGFOGLOHLCTHMSMTMTTCQD	1408
40	NOV6a	LGARRRPFER-LEFVGLVDLDG-----PDQQG	635
	Q63191	LGARRWPFQ-LEFVSLVDLDG-----PGQQG	634
	Q91641	SIHKPMPFK-VVFVSWCKSLWD-----CGIAA	487
	088799	AGYPVKPWREPQFCPLVCPKNSRYSLCAKPCPETCHPISTTQHCSDKCVEGCECDPGFIL	1597
	Q99ND0	AGYPVKPWREPQFCPLVCPKNSRYSLCAKPCPETCHPISTTQHCSDKCVEGCECDPGFIL	1595
	Q9BZ84	AGHAVKPWREPHEFCPMACPPNSKYSILCAKPCPDTC HSGFSGMFCSDRCEACECNPGFVL	1468
45	NOV6a	AGVDNVTLRDCSPTVTTERDREVSCNFERDTC SWYPGHLSDTHWRW-----	681
	Q63191	AGVDNVTLRDCNPMVTTESDQEVSCNFERDSCSWHTGHLTDAHWR-----	680
	Q91641	LDDISVSIGSCKISDRIPP-LPGKCTFEKNDGFGAGMAKEGYLAQNTRED-----P	538
	088799	SGSECVPSQCGCTSFQGRYFKLQEQWFNPDCKEICTCESHNHILCKPWCKAQEACSYK	1657
	Q99ND0	SGSECVPSQCGCTSFQGRYFKVQEQWFNPDCKEICTCESHNHILCKPWCKAQEACSYK	1655
50	Q9BZ84	SELECI PRSQCGCLHPAGSYFKVGERWYKPGCKELCVCESNNRIRCQPWRCRAQEF CGQ	1528
55	NOV6a	-----VESRGPDHDTTGQGHFVLLDPTDPLAWGHS AHLISRPOVPAAPTECLSF-----	731
	Q63191	-----VKS HGSQYDHTTGQGF FFLDPMDPPARGQ GALLITRPQVPVVPKECLSF-----	730
	Q91641	-----TFYTGPNGDHTSGVGYMYIEATN-MVFGQAKLISRPLRAVAGKQCLTF-----	587
	088799	NGVLGCHAQGAATCMVSGDPHYLTFD GALH HFMGTCTYVLTQPCWSKSOENNFVVSATNE	1717
	Q99ND0	NGVLGCHAQGAATCMVSGDPHYLTFD GALH HFMGTCTYVLTQPCWSKSOENNFVVSATNE	1715
	Q9BZ84	DGIYGCHAQGAATCTASGDPHYLTFD GALH HFMGTCTYVLTQPCWSRSQDSYFVVSATNE	1588

5	NOV6a	-----WYHLHGPOIGTIRLAMRREGEE-T-----HLWSRSGTQGNRWHEAWATL	774
	Q63191	-----WYHLHGPOIGTIRLAMRREGEDT-----LLWSRSGTHGNRWQAWVTLL	774
	Q91641	-----YYHMYGAGTGLINVYLITKEGDINKDT-----LLWTRKGEQSITW-----LK	628
	088799	IHDGNLEVSIVKAVHVQVFDLKI SMFKGQKVVLNNQRVVL PVWPSQGRVTIRLSGIFVLL	1777
	Q99ND0	IHDGNLEVSIVKAVHVQVFDLKI SMFKGQKVVLNNQRVVL PVWPSQGRVTIRLSGIFVLL	1775
	Q9BZ84	NRGGILEVSIVKAVHVTVFDLSISILLRGCKVMLNGHRVALPVWLAQGRVTIRLSSNLVLL	1648
10	NOV6a	SHQPGSHAQYQ---LLFEGLRDGVHGTMA-----LDD-----	803
	Q63191	HHQLQPSTKYQ---LLFEGLRDGVHGTMG-----LDD-----	803
	Q91641	-----AQMEYE-----	634
	088799	YTNFGLQVRVDGRHLVEVTVPSSSYTGSICGLCGNYNNNSMDDNLRADMKPAGNSLLLGAA	1837
	Q99ND0	YTNFGLQVRVDGRHLVEVTVPSSSYTGSICGLCGNYNNNSMDDNLRVDMKPAGNSLLLGAA	1835
	Q9BZ84	YTNFGLQVRVDGSHLVEVTVPSSSYGGQLCGLCGNYNNNSLDDNLRPDRKLADSMQLGAA	1708
15	NOV6a	-----VAVRPGPCWAPNYCSFEDSDCGFSPGGQGLWRRQANASGHAAWGPPT	850
	Q63191	-----MAVRPGPCWAAKRCFEDSDCGFSPGDWGLWTRQNNASGLGPWGPWI	850
	Q91641	-----	634
	088799	WKILEASDPGCFFLAGGKPSRCADSDMDVWTKKCAILMNPLGPFSSNCHEAVPPQASFS	1897
	Q99ND0	WKILEASDPGCFVLVGKPSRCADSDMDVWTKKCAILMNPLGPFSSNCHEAVPPQASFS	1895
	Q9BZ84	WKLPESEPGCFVLVGKPSRCQENSMADAWNKNCAILINPQGPFSQCHQVPPQSSFASC	1768
20	NOV6a	DHTTETAQGHYMVVDTS PDALP--RGQTASLTSKEHRPLAOPACLTFWYHGSRLSPGTLR	908
	Q63191	DHTTGTAGGHYMVVDTS PNLPL--KGHVASLTSEEHPPLSRPACLSFWYHLSFHNPGTLR	908
	Q91641	-----	634
	088799	VYGQCETNGDNLTFCHSLQAYASLCAQAGQVTTWRNSTFCPMRCPPRSSYNPCANSCPAT	1957
	Q99ND0	VYGQCETNGDNLTLCHSLQAYASLCAQAGQVTTWRNSTFCPMRCPPRSSYNPCANSCPAT	1955
	Q9BZ84	VHGQCGTKGDTTALCRSLQAYASLCAQAGQAPAWRNRTFCPMRCPPGSSSYSPCSSPCPDT	1828
25	NOV6a	VYLEERGRHQVLSLSAHGGLAWRLGSMVDQAEARAWRVVFEAVAAGVAHSYVAIDDLLOD	968
	Q63191	VFVEESTRRQELSTSGHGGFAWRLLGSVNVQAEQAWKVVFAMASGVEHSYMAIDDISLOD	968
	Q91641	-----SEQQHKIVFEAVRGISIRSDIAIDDLIFQON	664
	088799	CLTLSTPRDCP-TLPCVEGCECQSG--HILSGTTTCVPLRQCGCSDQDGSYHLLGESWYTE	2014
	Q99ND0	CLTLSTPRDCP-TLPCVEGCECQSG--HILSGTTTCVPLRQCGCSDQDGSYHLLGESWYTE	2012
	Q9BZ84	CSSINNPRDCPKALPCAESCECQKG--HILSGTSCVPLGQCGCTDPAGSYHPVGERWYTE	1886
30	NOV6a	GPCPQPGSDFES-----GLCGWSHLAWPGLGYSW---DWGGGATPSRYPQPPVDHTL	1019
	Q63191	GPCAQPGSDFES-----GLCGWSHLWPWGLGYSW---DWSSGATPSRYPSPVSDHTV	1019
	Q91641	GPCNDSSDPLQSS-----GYSD-----NFNNIEF-----	688
	088799	KTCITLCTCSAHSNITCSP TACKANHVCLRQEGLLRC-AAEMGECRISEDSQIVSFDDHS	2073
	Q99ND0	KTCITLCTCSAHSNITCSP TACKANHVCLRQEGLLRC-AAEMGECRISEDSQIVSFDDHS	2071
	Q9BZ84	NTCTRLCTCSVHNNITCFQSTCKPNQICWALDGLLRCRASGVGVCPGESHVVSFDGSN	1946
35	NOV6a	GTEAGHFAFFETGVLGPGGRAAWLRSEPLPATPASC-----LRFWYHMGFPEHFYKG	1071
	Q63191	GTEAGHFAFFETSVLGPGGQAALWGSEPLPATAVSC-----LHFWYMGFPAHFYKG	1071
	Q91641	-----	688
	088799	HPIQDTCTYILVKVCHENTNMPPFMISAKTDINTNGKNKTFGVYQLYIDIFNFHITLQKD	2133
	Q99ND0	HPIQDTCTYILVKVCHENTNMPPFMISAKTDINTNGKNKTFGVYQLYIDIFNFHITLQKD	2131
	Q9BZ84	HSIPDACTLVLVKVCHAMALPFPKISAKHEKEEGG-TEAFRLHEVYIDIDYDAQVTLOKG	2005
40	NOV6a	ELKVL-----LHSAQQLAVWGAGGHRRHQWLEAQVEVASAKEFQIVFEATILG	1119
	Q63191	ELRVL-----LSSTQQLAVWHRGGHLRDQWLQVQIEVSSSEEFQIVFEATILG	1119
	Q91641	-----	688
	088799	HLVLISLINDSIVTLPTTTHIPGVSVMTEDVYTIVTIKDEIQVKFESNNFLDVKIPASSN	2193
	Q99ND0	HLVLISLINDSIVTLPTTTHIPGVSVMTEDVYTIVTIKDEIQVKFESNNFLDVKIPASSN	2191
	Q9BZ84	HRVLI--N-SKQVTLPAISQIPGVSVKSSSIYSIVNIKIGVQVKFDGNHLLTEIPTIYY	2062
50	NOV6a	GQPA-----LGPIALDDVEYLAGQHCQOPAESPG-----	1148

	Q63191	QOPA-----LGPIALDDVBYLAGQHCKOPTPSQG-----	1148
	Q91641	-----	688
	O88799	GKVCGVCGNFGNGEEDELMTPSGELAEDEQEFMNSWKDKSMDPNCQ--KIEGQNLQVEQQ	2251
	Q99ND0	GKVCGVCGNFGNGEEDELMTPSGELAEDEQEFMNSWKDKSMDPNCQ--KIEGQNLQVEQQ	2249
5	Q9BZ84	GKVCGMCGNFNDEEDELMMPSDEVANSDSBFVNSWKDKDIDPSCQSLLVDEQQIPAEQQ	2122
	NOV6a	-----NTAAPGSVPAVVGSALLLMLLVLLG-----LGGRRWL	1181
	Q63191	-----RVAAPVSVPAVVG--ALLLFILLLG-----LGGWHWL	1179
	Q91641	-----	688
10	O88799	EIMNGKCRPIDFEKAQANCQTALQGPAAHACSSRVPIKPFILKCMNSFCEFREIFRALCD	2311
	Q99ND0	EIMNGKCRPIDFEKAQANCQTALQGPAAHACSSRVPIKPFILKCMNSFCEFREIFRALCD	2309
	Q9BZ84	ENPSGNCRAADLRAREKCEAALRAPVWAQCASRIDLTPFLVDCANTLCEFGGLYQALCQ	2182
	NOV6a	QKKGSCPFQSNTEATAPGFDNILENADGVTLPASVTSDF-----	1220
15	Q63191	QKQHLP--COSTDAAASGFDNILENADQVTLPESTITSNP-----	1216
	Q91641	-----	688
	O88799	SLQSFEDACQNGGLKPPILWRNSSEFCPLECPAHSHYTNCPLSCPPSCLDPDSDRCEGSGHKV	2371
	Q99ND0	SLQSFEDACQNGGLKPPILWRNSSEFCPLECPAHSHYTNCPLSCPPSCLDPDSDRCEGSGHKV	2369
20	Q9BZ84	ALQAFGATCQSQGLKPPILWRNSSEFCPLECPAYSSYTNCPLSCSPSCWDLDRCEG-----	2237
	NOV6a	-----	1220
	Q63191	-----	1216
	Q91641	-----	688
25	O88799	PATCREGCICQPDYVLLNDKCVLRSHCGCKDAQGVFIPAGKTIWISEDCTQSCCTCMKGSMR	2431
	Q99ND0	PATCREGCICQPDYVLLNDKCVLRSHCGCKDAQGVFIPAGKTIWISEDCTQSCCTCMKGSMR	2429
	Q9BZ84	-----	2237
	NOV6a	-----	1220
30	Q63191	-----	1216
	Q91641	-----	688
	O88799	CWDFQCPCPGTYCKNSNDGSSNCVKISLQCPAHSKFTDCLPPCHPSCSDPDGHCEGISTNA	2491
	Q99ND0	CWDFQCPCPGTYCKNSNDGSSNCVKISLQCPAHSKFTDCLPPCHPSCSDPDGHCEGISTNA	2489
	Q9BZ84	-----	2237
35	NOV6a	-----	1220
	Q63191	-----	1216
	Q91641	-----	688
	O88799	HSNCKEGCVCQPGYVLRNDKCVLRRIECGQHTQGGFIPAGKNWTSRGCSQSCDCMEGVIR	2551
	Q99ND0	HSNCKEGCVCQPGYVLRNDKCVLRRIECGQHTQGGFIPAGKSWTSRGCSQSCDCMEGVIR	2549
40	Q9BZ84	-----	2237
	NOV6a	-----	1220
	Q63191	-----	1216
	Q91641	-----	688
45	O88799	CQNFQCPSPGTYCQDIEDGTSNCANITLQCPAHSSFTNCLPPCQPSCDPEGHCGGSTTKA	2611
	Q99ND0	CQNFQCPSPGTYCQDIEDGTSNCANITLQCPAHSSFTNCLPPCQPSCDPEGHCGGSTTKA	2609
	Q9BZ84	-----	2237
	NOV6a	-----	1220
50	Q63191	-----	1216
	Q91641	-----	688
	O88799	PSACQEGCVCEPDYVVLNNKCVPRIECGCKDAQGVLI PADKIWINKGCTQTCACVTGTIHI	2671
	Q99ND0	PSACQEGCVCEPDYVVLNNKCVPRIECGCKDAQGVLI PADKIWINKGCTQTCACVTGTIHI	2669
	Q9BZ84	-----	2237
55	NOV6a	-----	1220
	Q63191	-----	1216

	Q91641	-----	688
	O88799	CRDFQCPSPGTYCKDIKDDASNCTEIILOCPDHSLYTHCLPSCLLSCSDPDGLCRGTSPEA	2731
	Q99ND0	CRDFQCPSPGTYCKDIKDDASNCTEITLQCPDHSLYTHCLPSCLPSCSDPDGLCRGTSPEA	2729
5	Q9BZ84	-----	2237
	NOV6a	-----	
	Q63191	-----	1220
	Q91641	-----	1216
10	O88799	PSTCKEGCVCDPDYVLSNDKCVLRIECGCKDAQGVLIIPAGKTWINRGCTQSCSCMGGAIQ	688
	Q99ND0	PSTCKEGCVCDPDYVLSNDKCVLRIECGCKDAQGVLIIPAGKTWINRGCTQSCSCMGGAIQ	2791
	Q9BZ84	-----	2789
		-----	2237
	NOV6a	-----	
15	Q63191	-----	1220
	Q91641	-----	1216
	O88799	CQNFKCPSEAYCQDMEDGNSNCTSIPLQCPAHSHYTNCLPTCQPSCSDPDGHCEGSSTKA	688
	Q99ND0	CQNFKCPSEAYCQDLEDGNSNCTSIPLQCPAHSHYTNCLPTCQPSCSDPDGHCEGSSTKA	2851
	Q9BZ84	-----	2849
		-----	2237
20	NOV6a	-----	
	Q63191	-----	1220
	Q91641	-----	1216
	O88799	PSACKEGCVCEPDYVMLNKNKCVPRIECGCKDTQGVLIIPADKTWINRGCTQSCTCRGGAIQ	688
	Q99ND0	PSACKEGCVCEPDYVMLNKNKCVPRIECGCKDTQGVLIIPADKTWINRGCTQSCTCRGGAIQ	2911
25	Q9BZ84	-----	2909
		-----	2237
	NOV6a	-----	
30	Q63191	-----	1220
	Q91641	-----	1216
	O88799	CQKYHCSSGTYCKDMEDDSSSCATITLQCPAHSHFTNCLPPCQPSCLDSEGHCEGSTTKA	688
	Q99ND0	CQKYHCSSGTYCKDMEDDSSSCATITLQCPAHSHFTNCLPPCQPSCLDSEGHCEGSTTKA	2971
	Q9BZ84	-----	2969
		-----	2237
35	NOV6a	-----	
	Q63191	-----	1220
	Q91641	-----	1216
	O88799	PSACQEGCVCEPDYVVLNKNKCVPRIECGCKDAQGVLIIPADKTWINRGCTQSCTCKGGAIQ	688
	Q99ND0	PSACQEGCVCEPDYVVLNKNKCVPRIECGCKDAQGVLIIPADKTWINRGCTQSCTCKGGAIQ	3031
40	Q9BZ84	-----	3029
		-----	2237
	NOV6a	-----	
45	Q63191	-----	1220
	Q91641	-----	1216
	O88799	CQKFQCPSETYCKDIEDGNSNCTRISLQCPANSNFTSCLPSCQPSCSNTDVHCEGSSPNT	688
	Q99ND0	CQKFQCPSETYCKDIEDGNSNCTRISLQCPANSNFTSCLPSCQPSCSNTDVHCEGSSPNT	3091
	Q9BZ84	-----	3089
		-----	2237
	NOV6a	-----	
50	Q63191	-----	1220
	Q91641	-----	1216
	O88799	LSSCREGCVQCQSGYVLHNDKCILRNQCGCKDAQGALIPEGKTWITSGCTQSCNCTGGAIQ	688
	Q99ND0	LSSCREGCVQCQSGYVLHNDKCILRNQCGCKDAQGALIPEGKTWITSGCTQSCNCTGGAIQ	3151
	Q9BZ84	-----	3149
		-----	2237
55	NOV6a	-----	
	Q63191	-----	1220
	Q91641	-----	1216
		-----	688

	088799	CQNFQCPLKTYCKDLKDGSSNCTNIPLQCPAHSRYTNCLPSCPPLCLDPEGLCEGTSPKV	3211
	Q99ND0	CQNFQCPLKTYCKDLKDGSSNCTNIPLQCPAHSRYTNCLPSCPPLCLDPEGLCEGTSPKV	3209
	Q9BZ84	-----AKV	2240
5	NOV6a	-----	1220
	Q63191	-----	1216
	Q91641	-----	688
	088799	PSTCREGCICQPGYLMHKNCVLRIFCGCKNTQGAFISADKTWISRGCTQSCTCPAGAIH	3271
	Q99ND0	PSTCREGCICQPGYLMHKNCVLRIFCGCKNTQGAFISADKTWISRGCTQSCTCSAGAIH	3269
10	Q9BZ84	PSACAEGCICQP-----	2252
	NOV6a	-----	1220
	Q63191	-----	1216
	Q91641	-----	688
15	088799	CRNFKCPSGTYCKNGDNGSSNCTEITLQCPNTSQFTDCLPSCVPSCSNRCEVTSPSPVSS	3331
	Q99ND0	CRNFKCPSGTYCKNGDNGSSNCTEITLQCPNTSQFTDCLPSCVPSCSNRCEVTSPSPVSS	3329
	Q9BZ84	-----	2252
	NOV6a	-----	1220
20	Q63191	-----	1216
	Q91641	-----	688
	088799	CREGCLCNHGFVFSSEDKCVPRTQCGCKDARGAIIIPAGKTWTSKGCTQSCACVEGNIQCQN	3391
	Q99ND0	CREGCLCNHGFVFSSEDKCVPRTQCGCKDARGAIIIPAGKTWTSKGCTQSCACVEGNIQCQN	3389
	Q9BZ84	-----GYVLSSEDKCVPRSQCGCKDAH-----	2273
25	NOV6a	-----	1220
	Q63191	-----	1216
	Q91641	-----	688
	088799	FQCPPETCYCKDNSEGSSTCTKITLQCPAHTQYTSCLPSCLPSCLDPEGLCKDISPKVPST	3451
30	Q99ND0	FQCPPETCYCKDNSEGSSTCTKITLQCPAHTQYTSCLPSCLPSCLDPEGLCKDISPKVPST	3449
	Q9BZ84	-----G-----GSIP-----	2278
	NOV6a	-----	1220
	Q63191	-----	1216
	Q91641	-----	688
35	088799	CKEGCVQCQSGYVLNSDKCVLRAECDCKDAQGALIPAGKTWTSPPGCTQSCACMGGAVQCQS	3511
	Q99ND0	CKEGCVQCQSGYVLNSDKCVLRAECDCKDAQGALIPAGKTWTSPPGCTQSCACMGGAVQCQS	3509
	Q9BZ84	-----L-----G-----	2280
40	NOV6a	-----	1220
	Q63191	-----	1216
	Q91641	-----	688
	088799	SQCPPGTYCKDNEDGNSNCAKITLQCPAHSLEFTNCLPCLPSCLDPDGLCKGASPKVPST	3571
	Q99ND0	SQCPPGTYCKDNEDGNSNCAKITLQCPAHSLEFTNCLPCLPSCLDPDGLCKGASPKVPST	3569
45	Q9BZ84	-----	2280
	NOV6a	-----	1220
	Q63191	-----	1216
	Q91641	-----	688
50	088799	CKEGCICQSGYVLSNNKCLLRNRCGCKDAHGALIPEDKTWVSRGCTQSCVCTGGSIQCLS	3631
	Q99ND0	CKEGCICQSGYVLSNNKCLLRNRCGCKDAHGALIPEDKTWVSRGCTQSCVCTGGSIQCLS	3629
	Q9BZ84	-----KSWVSSGCTEKCVCCTG-----	2296
	NOV6a	-----	1220
55	Q63191	-----	1216
	Q91641	-----	688
	088799	SQCPPGAYCKDNEDGSSNCARIPPQCPANSHYTDCTFPPCPPSCSDPEGHCEASGPRVLST	3691

	Q99ND0	FQCPPGAYCKDNEDGSSNCARIPQCPANSHYTDCFPSCPPSCSDPEGHCEASGPRVPST	3689
	Q9BZ84	-----	2296
5	NOV6a	-----	
	Q63191	-----	1220
	Q91641	-----	1216
	O88799	CREGCLCNPGFVLDLDRDKCVPRVECGCKDAQGALIPSGKTWTSPGCTQSCACMGGVVQCQS	688
	Q99ND0	CREGCLCNPGFVLDLDRDKCVPRVECGCKDAQGALIPSGKTWTSPGRTQSCACMGGVVQCQS	3751
10	Q9BZ84	-----	3749
	NOV6a	-----	2296
	Q63191	-----	1220
	Q91641	-----	1216
	O88799	SQCPPGTYCKDNEDGNSNCAKITLQCPHNSNYTDCLPFCLPSCLDPSALCGGTSPKGPST	688
15	Q99ND0	SQCPPGTYCKDNEDGNSNCAKITLQCPHNSNYTDCLPFCLPSCLDPSALCGGTSPKGPST	3811
	Q9BZ84	-----	3809
	NOV6a	-----	2296
	Q63191	-----	1220
20	Q91641	-----	1216
	O88799	CKEGCVCQPGYVLDKDKCILKIECGCRDTQGAVIPAGKTWLSTGCIQSCACVEGTIQCON	688
	Q99ND0	CKEGCVCQPGYVLDKDKCILKIECGCKDTQGAVIPAGKTWLSTGCIQSCACVEGTIQCON	3871
	Q9BZ84	-----	3869
	NOV6a	-----	2296
25	Q63191	-----	1220
	Q91641	-----	1216
	O88799	FQCPPGTYCNHNNNCAKIPLQCPAHSHFTSCLPSCPPSCANLDGSCEQTSPKVPSTCKEG	688
30	Q99ND0	FQCPPGTYCNHNNNCAKIPLQCPAHSHFTSCLPSCPPSCANLDGSCEQTSPKVPSTCKEG	3931
	Q9BZ84	-----	3929
	NOV6a	-----	2296
	Q63191	-----	1220
35	Q91641	-----	1216
	O88799	CLCQPGYFLNNGKCVLQTHCDCKDAEGGLVPAGKTWTSDKDCTQSCACTGGAVQCQNFQCP	688
	Q99ND0	CLCQPGYFLNNGKCVLQTHCDCKDAEGGLVPAGKTWTSDKDCTQSCACTGGAVQCQNFQCP	3991
	Q9BZ84	-----	3989
	NOV6a	-----	2296
40	Q63191	-----	1220
	Q91641	-----	1216
	O88799	LGTYCKDSGDGSSNCTKIHKGAMGDGVLMAAGGIRALQCPAHSHFTSCLPSCPPSCSNLDG	688
	Q99ND0	LGTYCKDSGDGSSNCTKIHKGAMGDGVLMAAGGIRALQCPAHSHFTSCLPSCPPSCSNLDG	4051
45	Q9BZ84	-----	4049
	NOV6a	-----	2296
	Q63191	-----	1220
	Q91641	-----	1216
	O88799	SCVESNFKAPSVCKKGCICQPGYLLNNDKCVLRIQCGCKDTQGGLIPAGRTWISSDCTKS	688
50	Q99ND0	SCVESNFKAPSVCKKGCICQPGYLLNNDKCVLRIQCGCKDTQGGLIPAGRTWISSDCTKS	4111
	Q9BZ84	-----	4109
	NOV6a	-----	2296
	Q63191	-----	1220
55	Q91641	-----	1216
	O88799	CSCMGGIIQCRDFQCPPGTYCKESNDSSRTCAKIPLQCPAHSHYTNCLPACSRSDTLDG	688
	Q99ND0	CSCMGGTIQCRDFQCPPGTYCKESNDSSRTCAKIPLQCPAHSHYTNCLPACSRSDTLDG	4171
			4169

	Q9BZ84	-----	2296
	NOV6a	-----	1220
	Q63191	-----	1216
5	Q91641	-----	688
	O88799	HCEGTS PKVPSPCKEGCLCQPGYVVHNH KCVLQIHCGCKDAQGGFVPAGKTWISRGCTQS	4231
	Q99ND0	HCEGTS PKVPSPCKEGCLCQPGYVVHNH KCVLQIHCGCKDAQGGFVPAGKTWISRGCTQS	4229
	Q9BZ84	-----	2296
10	NOV6a	-----	1220
	Q63191	-----	1216
	Q91641	-----	688
	O88799	CACVGGAVQCHNFTCPTGTQCQNSSCSKITVQCPAH SQYTTCLPSCLPSCFDPEGLCGGA	4291
	Q99ND0	CACVGGAVQCHNFTCPTGTQCQNSSCSKITVQCPAH SHYTTCLPSCLPSCFDPEGLCGGA	4289
15	Q9BZ84	-----	2296
	NOV6a	-----	1220
	Q63191	-----	1216
	Q91641	-----	688
20	O88799	SPRAPSTCREGCVCEADYVLREDKCVLR TQCGCKDAQGD LIPANKTWL TRGCAQKCTCKG	4351
	Q99ND0	SPRAPSTCREGCVCEADYVLREDKCVLR TQCGCKDAQGD LIPANKTWL TRGCAQKCTCKG	4349
	Q9BZ84	-----	2296
	NOV6a	-----	1220
	Q63191	-----	1216
	Q91641	-----	688
25	O88799	GNIHCWNFKCPLGTECKDSVDGGSNCTKIALQCPAH SHHTYCLPSCIPSCSNVNDRC EST	4411
	Q99ND0	GNIHCWNFKCPLGTECKDSVDGGSNCTKIALQCPAH SHHTYCLPSCIPSCSNVNDRC EST	4409
	Q9BZ84	-----	2296
30	NOV6a	-----	1220
	Q63191	-----	1216
	Q91641	-----	688
	O88799	SLQRPSTCIEGCLCHSGFVFSKDKCVPR TQCGCKDSQGT LIPAGKNWIT TGCSQRCTCTG	4471
35	Q99ND0	SLQRPSTCIEGCLCHSGFVFSKDKCVPR TQCGCKDSQGT LIPAGKNWIT TGCSQRCTCTG	4469
	Q9BZ84	-----	2296
	NOV6a	-----	1220
	Q63191	-----	1216
	Q91641	-----	688
40	O88799	GLVQCHDFQCPSGAECQDIEDGNSNCVEITVQCPAH SHYSKCLPPCQPSCSDPDGHCEGT	4531
	Q99ND0	GLVQCHDFECPSGAECQDIEDGNSNCVEITVQCPAH SHYSKCLPPCQPSCSDPDGHCEGT	4529
	Q9BZ84	-----	2296
45	NOV6a	-----	1220
	Q63191	-----	1216
	Q91641	-----	688
	O88799	SPEAPSTCEEGCVCEPDYVLSNDKCVPSSECGCKDAHGV LIPESKTWVSRGCTKNCTCKG	4591
	Q99ND0	SPEAPSTCEEGCVCEPDYVLSNDKCVPSSECGCKDAHGV LIPESKTWVSRGCTKNCTCKG	4589
50	Q9BZ84	-----	2296
	NOV6a	-----	1220
	Q63191	-----	1216
	Q91641	-----	688
55	O88799	GTVQCHDFSCPTGSRCLDNNEGNSNCVTYALKCPAH SLYTNCLPSCLPSCSDPEGLCGGT	4651
	Q99ND0	GTVQCHDFSCPTGSRCLDNNEGNSNCVTYALKCPAH SLYTNCLPSCLPSCSDPEGLCGGT	4649
	Q9BZ84	-----	2296

	NOV6a	-----	
	Q63191	-----	1220
	Q91641	-----	1216
5	088799	SPEVPSTCKEGCICQSGYVLHKNKCMRLRIHCDCKDFQGS LIKTGQTWISSGCSKICTCKG	688
	Q99ND0	SPEVPSTCKEGCICQSGYVLHKNKCMRLRIHCDCKDFQGS LIKTGQTWISSGCSKICTCKG	4711
	Q9BZ84	-----	4709
		-----	2296
	NOV6a	-----	
10	Q63191	-----	1220
	Q91641	-----	1216
	088799	GFFQCQSYKCPSGTQCEESE DGSSNCVSSTMKCPANS LYTHCLPTCLPSCSNPDGRCEGT	688
	Q99ND0	GFFQCQSYKCPSGTQCEESE DGSSNCVSSTMKCPANS LYTHCLPTCLPSCSNPDGRCEGT	4771
	Q9BZ84	-----	4769
		-----	2296
	NOV6a	-----	
	Q63191	-----	1220
	Q91641	-----	1216
20	088799	SHKAPSTCREGCVCQPGYLLNKDTCVHKNQCGCKDIRGNIIPAGNTWISSDCTQSCACTD	688
	Q99ND0	SHKAPSTCREGCVCQPGYLLNKDTCVHKNQCGCKDIRGNIIPAGNTWISSDCTQSCACTD	4831
	Q9BZ84	-----	4829
		-----	2296
	NOV6a	-----	
	Q63191	-----	1220
	Q91641	-----	1216
25	088799	GVIQCQNFVCPSGSHCQYNEDGS-SDCAANKLERCTIFGDPY YLTFDGFTYHFLGRMNYY	688
	Q99ND0	GVIQCQNFVCPSGSHCQYNEDGS-SDCAANKLERCTIFGDPY YLTFDGFTYHFLGRMNYY	4890
	Q9BZ84	GAIQCQDFRCPSGSHCQLTSDNSNSNCVSDKSEQCSVYGDPRYLTFDGFSYRLQGRMTYV	4888
		-----	2356
	NOV6a	-----	
	Q63191	-----	1220
	Q91641	-----	1216
30	088799	LIKTVDKLPRGIEPLIMEGRNKISP-KGSSTLHEVTTIVGYKIQLQEELVVLVNDKVA	688
	Q99ND0	LIKTVDKLPRGIEPLIMEGRNKISP-KGSSTLHEVTTIVGYKIQLQEELVVLVNDKVA	4949
35	Q9BZ84	LIKTVDVLPPEGVEPLLVEGRNKMDDPRSSIFLQEVITTVYGYKVQLQAGLELVVNQKMA	4947
		-----	2416
	NOV6a	-----	
	Q63191	-----	1220
	Q91641	-----	1216
40	088799	VPYNPNEHLRVMLRAQRLLLVTD FEMVLDFDGKHS AVISLP TTYRGLTRGLCGNYDRDQS	688
	Q99ND0	VPYNPNEHLRVMLRAQRLLLVTD FEMVLDFDGKHS AVISLP TTYRGLTRGLCGNYDRDQS	5009
	Q9BZ84	VPYRPNEHLRVTLWGQRLYLVTDFELVVSFGGRKN AVISLP S MYEGLVSGLCGNYDKNRK	5007
		-----	2476
	NOV6a	-----	
45	Q63191	-----	1220
	Q91641	-----	1216
	088799	NELMLPSGVLTSNVHVF GNSWEVKQAHAFFRFPRALPEDEERD-----EEPDLLQSECSQ	688
	Q99ND0	NELMLPSGVLTSNVHVF GNSWEVKQAHAFFRFPRALPEDEERD-----EEPDLLQSECSQ	5064
	Q9BZ84	NDMMLPSGALTQNLNTFGNSWEVKTEDALLRFPRAIPAE EEGQGAELGLRTGLQVSECSQ	5062
50		-----	2536
	NOV6a	-----	
	Q63191	-----	1220
	Q91641	-----	1216
55	088799	EQTALISSTQACRVLD P QGPFAACHQIIAEPF EQRCMLDMCTGWKTKEEEELRCRVLS	688
	Q99ND0	EQTALISSTQACRVLD P QGPFAACHQIIAEPF EQRCMLDMCTGWKTKEEEELRCRVLS	5124
	Q9BZ84	EQLASN-STQACRVLD P QGPFAACHQTV AEPFQEHCVLDLCSAQDPREQEELRCQVLS	5122
		-----	2595

	NOV6a	-----	1220
	Q63191	-----	1216
	Q91641	-----	688
5	O88799	GYAIIICQEAGANMTGWRDHTHCAMTCPANTVYQRCMTPCPASCACAFVTPKVCCEGPCVEGC	5184
	Q99ND0	GYAIIICQEAGANMTGWRDHTHCAMTCPANTVYQRCMTPCPASCACAFVTPKVCCEGPCVEGC	5182
	Q9BZ84	GWAAAF-----	2601
	NOV6a	-----	1220
	Q63191	-----	1216
10	Q91641	-----	688
	O88799	ASLPGYIYSDTQSLPVTHCGCTADGIYYKLGDSEFVTNDCSQHCTCASQGILLCEPYGCRA	5244
	Q99ND0	ASLPGYIYSDTQSLPVTHCGCTADGIYYKLGDSEFVTNDCSQHCTCASQGILLCEPYGCRA	5242
	Q9BZ84	-----	2601
	NOV6a	-----	1220
	Q63191	-----	1216
	Q91641	-----	688
15	O88799	GESCMVANFTRGCFQDSPCLQNPCHNDGRCEEQGATFICHCDFGYGGEFCTEPQDITTRK	5304
	Q99ND0	GESCMVANFTRGCFQDSPCLQNPCHNDGRCEEQGATFICHCDFGYGGEFCTEPQDITTRK	5302
20	Q9BZ84	-----	2601
	NOV6a	-----	1220
	Q63191	-----	1216
	Q91641	-----	688
25	O88799	KIEASSLVAILPGVLVLMVLVPVLLPRVYVYMATRTTMGRRRMKRKEKKLLRQSRLRLEDA	5364
	Q99ND0	KIEASSLVAILPGVLVLMVLVPVLLPRVYVYMATRTTMGRRRMKRKEKKLLRQSRLRLEDA	5362
	Q9BZ84	-----	2601
	NOV6a	-----	1220
30	Q63191	-----	1216
	Q91641	-----	688
	O88799	DVPEPTFKATEF	5376
	Q99ND0	DVPEPTFKATEF	5374
35	Q9BZ84	-----	2601

Domain results for NOV6 were collected from the Pfam database, and then identified by the Interpro domain accession number. The results are listed in Table 6G with the statistics and domain description. These results indicate that the NOV6 polypeptides have properties similar to those of other proteins known to contain these domains.

Table 6G. Domain Analysis of NOV6

PSSMs Producing Significant Alignments	Score (bits)	E Value
MAM: domain 4 of 6, from 660 to 813	192.5	6.7e-54

MAM	CdFEdgshPfCgWsqdsgddgddlqWtrvnsatggstgprgdhttGn		
NOV6a	+ + +++++ + ++ ++ ++ +++++ +		
	CNFERDT---CSWYPGHLSD---THWRWVESR-----GPDHDHTTGO		
NOV6a	GhymyvdtssgllqeGqkArLlSpplppnrspcCLtFwYhmyGsgvgtp		
	++ +++++ + + ++ + + ++ +++++ + + +++ ++ ++		
	GHFVLLDPTDPL-AWGHSALLSRPQVPAAPT-ECLSFWYHLHGPOIGT-		
NOV6a	gLnvyvreng.e.tllWsrsgHqggqWllaevtlpt..fstkpfqvvFegt		
	+++++ +++++ + +++ ++++ ++++ ++++++ +++++ +++		
	-LRLAMRREGEEeTHLWSRSGTQGNRWHEAWATLSHqpGSHAQYQLLFEGL		
NOV6a	rgggsrGgIALDDIslsthiiegpCnq (SEQ ID NO:77)		
	+ +++ ++ + + ++ +++ ++		
	R-DGYHGTMALDDVAVR---PGPCWA (SEQ ID NO:20)		
MAM: domain 6 of 6, from 977 to 1142		199.2	6.4e-56
MAM	CdFEdgshPfCgWsqdsgddgddlqWtrvnsatgg.stgprgdhttG		
NOV6a	+ ++ + + ++ ++++++ ++ ++++++ ++++++		
	CDFESG---LCGWSHLAWPGLGGYSWDWGGGATPSrYPQPPVDHTLG		
NOV6a	n..GhymyvdtssgllqeGqkArLlSpplppnrspcCLtFwYhmyGsgv		
	++ ++ +++++ + + ++ ++ + + +++++ + + + ++ +++++		
	TeaGHFAFFETGVLG-PGGRAAWLRSEPLPATPAS--CLRFWYHMGFPFH		
NOV6a	gtpg.Lnvyvreng.e.tllWsrsgHqggqWllaevtlptfstkpfqvvFe		
	++++ +++ + +++ + ++ + ++ +++++ + +++++ +		
	FYKGeLKVLLHSAQGqLAVWVGAGGHRHQWLEAQVEVA--SAKEFQIVFE		
NOV6a	gtrg.ggsrGgIALDDIslsthiiegpCnq (SEQ ID NO:78)		
	++ +++++ + + + +++++ +++ +		
	ATLGgQPALGPALDDVEYLA-GQHCQQ (SEQ ID NO:20)		

The NOV6 disclosed in this invention may be expressed in a variety of tissues.

The protein similarity information, expression pattern, and map location for the apical endosomal glycoprotein-like protein and nucleic acid disclosed herein suggest that this protein may have important structural and/or physiological functions characteristic of the apical endosomal glycoprotein family. Therefore, the nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications and as a research tool. For example, the compositions of the present invention will have efficacy for treatment of patients suffering from: endometriosis, fertility and other diseases, disorders and conditions of the like.

The novel nucleic acid encoding the apical endosomal glycoprotein-like protein of the invention, or fragments thereof, are useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed. These materials are further useful in

the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. The disclosed NOV6 protein has multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, a contemplated NOV6 epitope is from about amino acids 20 to 150. In another embodiment, a contemplated NOV6 epitope is from about amino acids 150 to 200. In alternative embodiments, contemplated NOV6 epitopes include from about amino acids 205 to 310, 320 to 355, 375 to 410, 410 to 440, 440 to 550, 570 to 740, 740 to 800, 800 to 950, 950 to 990, 995 to 1025, 1045 to 1070, 1100 to 1120, 1125 to 1160, and 1175 to 1210.

NOV7

Another NOVX protein of the invention, referred to herein as NOV7, includes three novel ADAM13-like proteins. The disclosed proteins have been named NOV7a, NOV7b, and NOV7c. The ADAM family proteins contain a metalloprotease domain, a disintegrin domain, and a cystein-rich domain. The proteins are human homologs of mouse meltrin-alpha, which are involved in mytube formation

The NOV7 proteins disclosed herein are predicted to localize extracellularly. Therefore, it is likely that these proteins are accessible to a diagnostic probe, and for the various therapeutic applications described herein.

At least the NOV7a protein disclosed in this invention maps to chromosome 20. This information was assigned using OMIM, the electronic northern bioinformatic tool implemented by CuraGen Corporation, public ESTs, public literature references and/or genomic clone homologies.

NOV7a

In one embodiment, a NOV7 variant is NOV7a (alternatively referred to herein as CG50367-01), which encodes a novel ADAM13-like protein and includes the 2762 nucleotide sequence (SEQ ID NO:21) shown in Table 7A. An open reading frame for the mature protein was identified beginning with an ATG codon at nucleotides 3-5 and ending with a TGA codon at nucleotides 2745-2747. Putative untranslated regions downstream from the termination codon

and upstream from the initiation codon are underlined in Table 7A, and the start and stop codons are in bold letters.

Table 7A. NOV7a Nucleotide Sequence (SEQ ID NO:21)

CTATGGGCTGGAGGCCCCGGAGAGCTCGGGGGACCCCGTTGCTGCTGCTGCTACTACTGCTGCTGCTCTGGCCAG
TGCCAGGCGCCGGGGTCTTCAAGGACATATCCCTGGGCAGCCAGTCACCCCGCACTGGGTCTGGATGGACAAC
CCTGGCGCACCGTCAGCTCTGAGGAGGACCGGCTCTCGAAGCCAGACATGGGGCTGGTGGCCCTGGAGGCTGAAGGCC
AGGAGCTCCTGCTTGAGCTGGAGAGAAGAACACAGGCTGCTGGCCCCAGGATACATAGAAACCCACTACGGCCCCAG
ATGGGCAGCCAGTGGTGTGGCCCCCAACCACAGGATCATTTGCCACTACCAAGGGCGAGTAAGGGGCTTCCCCG
ACTCCTGGGTAGTCTCTGCACTGTCTGGAATGAGTGGCCCTGATCACCTCAGCAGGAATGCCAGCTATTATC
TGCGTCCCTGGCCACCCCGGGGCTCCAAGGACTTCTCAACCCACGAGATCTTTCGGATGGAGCAGCTGCTCACCT
GGAAAGGAACCTGTGGCCACAGGGATCTGGGAACAAAGCGGGCATGACAGCCCTTCTGGTGGTCCCCAGAGCA
GGGGCAGGCGAGAAGCGCGCAGGACCCGGAAGTACCTGGAAGTGTACATTGTGGCAGACCACCCCTGTTCTTGA
CTCGGCACCGAACTTGAACCACACAAACAGCGTCTCCTGGAAGTCGCCAACTACGTGGACCAGCTTCTCAGGA
CTCTGGACATTAGGTGGCGCTGACCGGCTGGAGGTGTGGACCGAGCGGGACCGCAGCCGCTCACGAGGACG
CCAACGCCACGCTCTGGGCCTTCTGCACTGGCGCCGGGGGCTGTGGGCGCAGCGGCCCAAGACTCCGCGCAGC
TGCTCACGGGCGCCGCGCTTCCAGGGCGCCACAGTGGGCCTGGCGCCCGTCGAGGGCATGTGCCGCGCCGAGAGCT
CGGGAGGCGTGAGCAGGACCACTCGGAGCTCCCCATCGGCGCCGCGAGCCACCATGGCCCATGAGATCGGCCACA
GCCTCGGCCTCAGCCACGACCCCGACGGCTGCTGCGTGGAGGCTGCGGCCGAGTCCGGAGGCTGCGTCATGGCTG
CGGCCACCGGGCACCCCTTTCCGCGCGTGTTCAGCGCTGCAGCCGCGCCAGCTGCGCGCTTCTTCCGCAAGG
GGGGCGGCGCTTGCTCTCCAATGCCCGGACCCCGACTCCCGGTGCCGCGCGCGCTCTGCGGGAACGGCTTCG
TGGAAGCGGGCGAGGAGTGTGACTGCGGCCCTGGCCAGGATGCCGCGACCTCTGCTGCTTTGCTCACAAGTGTCT
CGCTGCGCCCGGGGGCCAGTGCGCCACGGGGACTGTGCGTGGCTGCTGCTGAAGCCGGCTGGAGCGCTGT
GCCGCCAGGCCATGGGTGACTGTGACCTCCCTGAGTTTTCACGGCCACCTTCTCCACTGTCCCCAGACGTTT
ACCTACTGGACGGCTCACCTGTGCCAGGGGCGAGTGGCTACTGCTGGGATGGCGCATGTCCACGCTGGAGCAGC
AGTGCCAGCAGCTCTGGGGGCTGGCTCCACCCAGCTCCCGAGGCTGTTTTCCAGTGGTGAACCTCTGCGGGAG
AGCTGCAGTGCCAGGGTGGAAAGCCAGCCTGCTGCGACCGCACATGGTGCCAGTGGACTCTACCGTTACCTAG
ATGGCCAGGAAGTGACTTGTGCGGGAGCCTTGGCACTCCCCAGTGCCAGCTGGACCTGCTTGGCTGGGCTGG
TAGAGCCAGGACCCAGTGTGGACCTAGAATGGTGTGCCAGAGCAGGCGCTGCAGGAAGAATGCCTTCCAGGAGC
TTCAGCGCTGCCTGACTGCCTGCCACAGCCACGGGGTTTGCAATAGCAACCATAACTGCCACTGTGCTCCAGGCT
GGGCTCCACCTTCTGTGACAAGCCAGCCTTTGGTGGCAGCATGGACAGTGGCCCTGTGCGAGGCTGAAAACCATG
ACACCTTCTGCTGGCCATGCTCCTCAGCGTCTGCTGCTGCTGCCAGGGGCGGCGCTGGCCTGGTGTGCT
ACCGACTCCCAGGAGCCCATCTGCAGCGATGACAGCTGGGGCTGCAGAAGGGACCTTGGTGCAGTGGCCCCAAG
ATGGCCACACAGGGACCACCCCTGGGCGCGTTACCCCATGGAGTTGGGCCCCACAGCCACTGGACAGCCCT
GGCCCTTGGCCCCAGGGGCTCTGCTGACCATATTACAACATTTACCTCCACCATTTCTCCAGACCCCTGAGA
ACTCTCATGAGCCAGCAGCCACCCCTGAGAAGCCTCTGCCAGCAGTCTCGCCTGACCCCAAGGTGGTTCCTTG
CAGCCTGGGGCCCCAGTCCCTTTAGGGGACAACATATCTCCTCATTCTCAGCAGATCAAGTCCAGATGCCAAGAT
CCTGCTCTGTGGCGAAACCTGGGGAGGCCACGTGGGAAGGAAAGAGGGCTCTAAGAGGGGAGGCCCCAGACTGG
GGGAGAGGCTGTCTGGAGCCAGGATCACCTGGCTGTGCTGCAGAACTGGAGAAGAGAAGCTCAGCAGAAAGGA
GCTGCGATGGGGCCAACAGCAGAAAAGCAGGAGGCACGCAGAAGTGACTGGGAAGCAGGAGG

5 The sequence of NOV7a was derived by laboratory cloning of cDNA fragments, by *in silico* prediction of the sequence. The cDNA fragments covering either the full length of the DNA sequence, or part of the sequence, or both, were cloned. *In silico* prediction was based on sequences available in CuraGen's proprietary sequence databases or in the public human sequence databases, and provided either the full length DNA sequence, or some portion thereof.

The DNA sequence and protein sequence for a novel transmembrane-like gene were obtained by SeqCalling™ Technology and are reported here as NOV7a. These methods used to amplify NOV7a cDNA are described in Example 2.

The NOV7a polypeptide (SEQ ID NO:22) encoded by SEQ ID NO:21 is 914 amino acid residues in length and is presented using the one-letter amino acid code in Table 7B. The SignalP, Psort and/or Hydropathy results predict that NOV7a has a signal peptide and is likely to be localized extracellularly at the plasma membrane with a certainty of 0.4600. In alternative embodiments, a NOV7a polypeptide is located to the microbody (peroxisome) with a certainty of 0.1026, the endoplasmic reticulum (membrane) with a certainty of 0.1000, or the endoplasmic reticulum (lumen) with a certainty of 0.1000. The SignalP predicts a likely cleavage site for a NOV7a peptide between amino acid positions 29 and 30, i.e. at the dash in the sequence GAG-VL.

Table 7B. Encoded NOV7a Protein Sequence (SEQ ID NO:22)

MGWRPRRARGTPLLLLLLLLLLLWVPVGAGVLQGHIPGQPVTPHWVLDGQPWRTVSLEEPVSKPDMGLVALEAEG
QELLLELEKHNHRLAPGYIETHYGPDPVVLAPNHTDHCHYQGRVRGFPDSWVVLCTCSGMSGLITLSRNASY
YLRPWPPRGSKDFSTHEIFRMEQLLTWKGTGCHRDPGNKAGMTSLPGGPQSRGRREARRTRKYLELYIVADHTL
FLTRHRNLNHTKQRLLEVANYVDQLLRTLDIQVALTGLEVWTERDRSRVTQDANATLWAFWLQWRRGLWAQRPHD
SAQLLTGRAFGQATVGLAPVEGMCRAESSGGVSTDHSELP I GAAATMAHEIGHSLGLSHDPDGCCVEAAAESGG
CVMAAATGHPFPRVFSACSRRLRAFFRKGGGACLSNAPDPGLPVPPALCGNGFVEAGEECDGCGPQGECDLCC
FAHNCSLRPGAQCAHGDCCVRCLLKPA GALCRQAMGDCDLPEFCTGTSSHCPPDVYLLDGS PCARGSGYCWDGA
CPTLEQQCCQQLWGP GSHPAEACFQVVNSAGDAHGNCQG DSEGHFLP CAGRDALCGKLQCQGGKPSLLAPHMVP
VDSTVHLDGQEVTCRGALALPSAQLDLLGLGLVEPGTQC GPRMV CQSRR CRKNAFQELQRCLTACHSHGVCNSN
HNCHCAPGWAPPFCDKPGFGGSGMDSGPVQAENHDTFLLAMLLSVLLPLLPGAGLAWCCYRLPGAHLQRC SWGCR
RDPACSGPKDGPHRDHPLGVDHVPMELGPTATGQWPWPLAPGAPADHIHNIYPPFFLPDPENSHEPSSHPEKPLPA
VSPDPQKGLSAAWGPSPLGDNISSFSADQVQMPRSCLCGEPWGGHVGRKEGSKRGGPRLGERPVWSPGSPGCA
AELEKRSSAERSWHGANSRKAGGTOK

15 NOV7b

In an alternative embodiment, a NOV7 variant is NOV7b (alternatively referred to herein as CG50367-02), which includes the 2705 nucleotide sequence (SEQ ID NO:23) shown in Table 7C. An open reading frame for the mature protein was identified beginning with an ATG codon at nucleotides 3-5 and ending with a TGA codon at nucleotides 2688-2690. The start and stop codons of the open reading frame are highlighted in bold type. Putative untranslated regions are underlined and found upstream from the initiation codon and downstream from the termination codon.

CTATGGGCTGGAGGCCCGGAGAGACTCGGGGGACCCCGTTGCTGCTGCTGCTACTACTGCTGCTGCTCTGGCCAG
TGCCAGGCGCCGGGGTGCTTCAAGGACATATCCCTGGGCAGCCAGTCACCCCGCACTGGGTCTGGATGGACAAC
CCTGGCGCACCGTCAGCCTGGAGGAGCCGGTCTCGAAGCCAGACATGGGGCTGGTGGCCCTGGAGGCTGAAGGCC
AGGAGCTCCTGCTTGAGCTGGAGAAGAACCCACAGGTGCTGCGCCCAAGGATACATAGAAAACCACTACGGCCAG
ATGGGCAGCCAGTGGTGTGCGCCCCAACCCACACGGATCACTTGCCACTACCAAGGGCGAGTAAGGGGCTTCCCCG
ACTCCTGGGTAGTCTCTGCACTGCTCTGGGATGAGTGGCCTGATACCCCTCAGCAGGAATGCCAGCTATTATC
TGCGTCCCTGGCCACCCCGGGGCTCCAAGGACTTCTCAACCACAGAGATCTTTCCGATGGAGCAGCTGCTCACCT
GGAAAGGAACCTGTGGCCACAGGGATCCTGGGAACAAAGCGGGCATGACCAGCCTTCTGGTGGTCCCCAGAGCA
GGGGCAGGCGAGAAGCGCGCAGGACCCGGAAGTACCTGGAACTGTACATTGTGGCAGACCACACCTGTCTTCTGA
CTCGGCACCGAAACTTGAACCACACCAAACAGCGTCTCCTGGAAGTCGCCAACTACGTGGACCAGCTTCTCAGGA
CTCTGGACATTAGGTGGCGCTGACCGGCCTGGAGGTGTGGACCGAGCGGGACCGCAGCCGCGTCAAGCAGGAGC
CCAAGCCACGCTCTGGGCCCTTCTGTCAGTGGCGCCGGGGGCTGTGGGCGCAGCGGCCCCACGACTCCGCGCAGC
TGCTCACGGGCGCGCCTTCCAGGGCGCCACAGTGGGCCTGGCGCCCGTCGAGGGCATGTGCCGCGCCGAGAGCT
CGGGAGGCGTGAGCAGGACCACTCGGAGCTCCCCATCGGCGCCGACGCCACCATGGCCCATGAGATCGGCCACA
GCCTCGGCCTCAGCCACGACCCCGACGGCTGCTGCGTGGAGGCTGCGGCCGAGTCCGGAGGCTGCGTCAATGGCTG
CGGCCACCGGGCACCCGTTTCCGCGCGTGTTCAGCGCCTGACGCCGCGGCCAGCTGCGCGCCTTCTTCCGCAAGG
GGGGCGGCGCTTGCTCTCCAATGCCCGGACCCCGGACTCCCGGTGCCGCCGGCGCTCTGCGGGAACGGCTTCG
TGGAAGCGGGCGAGGAGTGTGACTGCGGCCCTGGCCAGGAGTGGCGCGACCTCTGCTGCTTTGCTCACAACTGCT
CGCTGCGCCCGGGGGGCCAGTGCGCCACGGGGACTGCTGCGTGCCTGCTGCTGAGCCGGCTGGAGCGCTGT
GCCGCCAGGCCATGGGTGACTGTGACCTCCCTGAGTTTTGCACGGGCACCTCTCCCACTGTCCCCCAGACGTTT
ACCTACTGGACGGCTCACCTGTGCCAAGGGCAGTGGCTACTGCTGGGATGGCGCATGTCCCACTGTCCCGAGC
AGTGCCAGCAGCTCTGGGGGCTGGCTCCACCCAGCTCCCGAGGCTGTTTCCAGGTGGTGAACCTGTGCGGAG
ATGCTCATGGAACTGCGGCCAGGACAGCGAGGGCACTTCTGCTGCTGTCAGGGAGGGATGCCCTGTGTGGGA
AGTCTCAGTGGCCAGGGTGGAAAGCCAGCCTGCTCGCACCGCACATGGTGCCAGTGGACTCTACCGTTACCTAG
ATGGCCAGGAAGTGACTTGTGCGGGAGCCTTGGCACTCCCCAGTGCCAGCTGGACCTGCTTGGCCTGGGCCTGG
TAGAGCCAGGCACCCAGTGTGACCTAGAATGGTGTGCCAGAGCAGGCGCTGCAGGAAGAATGCCCTTCCAGGAGC
TTAGCGCTGCCTGACTGCCTGCCACAGCCACGGGGTTTGAATAGCAACCATAACTGCCACTGTGCTCCAGGCT
GGCTCCACCTTCTGTGACAAGCCAGGCTTTGGTGACATGGACAGTGGACAGTGGCCCTGTGACGGCTGAAAACCATG
CACCTTCTGCTGGCCATGCTCCTCAGCGTCTCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCT
CCGACTCCAGGAGCCCATCTGCAGCGATGCAGCTGGGGCTGCAAGGGACCTGCTGCTGCTGCTGCTGCTGCTGCTGCT
TGGCCACACAGAGACCACCCCTGGGCGGCGTTACCCCATGGAGTTGGGCCCCACAGCCACTGGACAGCCCT
GCCCCCTGGACCCTGAGAACTCTCATGAGCCAGCAGCCACCTGAGAAGCCTCTGCCAGCAGTCTGCCTGACC
CCAAGGTGGTTCCCTTGCAGCCTGGGGCCCCAGTCTTTAGGGGACAACATATCCTCCTCATTTCTCAGCAGATC
AGTCCAGATGCCAAGATCCTGCCTCTGTGGCGAACCTGGGGAGGCCACGTGGGAAGGAAAGAGGGCTCTAAGA
GGGAGGCCCCAGACTGGGGGAGAGGCCTGTCTGGAGCCAGGATCACCTGGCTGTGCTGCAGAACTGGAGAAGA
AAGCTCAGCAGAAAGGAGCTGGCATGGGGCCAACAGCAGAAAGCAGGAGGCACGCAGAACTGACTGGGAAGCA
GAGG

The DNA sequence and protein sequence for a novel stabilin-like gene were obtained by SeqCalling™ Technology and are reported here as NOV7b. These methods used to amplify NOV7b cDNA are described in Example 2.

embodiments, a NOV7b polypeptide is located to the microbody (peroxisome) with a certainty of 0.1011, the endoplasmic reticulum (membrane) with a certainty of 0.1000, or the endoplasmic reticulum (lumen) with a certainty of 0.1000. The SignalP predicts a likely cleavage site for a NOV7b peptide between amino acid positions 29 and 30, i.e. at the dash in the sequence GAG-VL.

10

NOV7c

15 as CG50367-03), which includes the 2642 nucleotide sequence (SEQ ID NO:25) shown in Table 7E. An open reading frame for the mature protein was identified beginning with an ATG codon at nucleotides 3-5 and ending with a TGA codon at nucleotides 2625-2627. The start and stop codons of the open reading frame are highlighted in bold type. Putative untranslated regions are underlined and found upstream from the initiation codon and downstream from the termination
20 codon.

Table 7E. NOV7c Nucleotide Sequence (SEQ ID NO:25)

CTATGGGCTGGAGGCCCCGGAGAGCTCGGGGGACCCGTTGCTGCTGCTGCTACTACTGCTGCTGCTCTGGCCAG
 TGCCAGGCGCCGGGGTGTTC AAGGACATATCCCTGGGCAGCCAGTCACCCCGCACTGGGTCTGGATGGACAAC
 CCTGGCGCACCGTCAGCCTGGAGGAGCCGGTCTCGAAGCCAGACATGGGGCTGGTGGCCCTGGAGGCTGAAGGCC
 AGGAGCTCCTGCTTGAGCTGGAGAAGAACCACAGGCTGCTGGCCCCAGGATACATAGAAACCCACTACGGCCAG
 ATGGGCAGCCAGTGGTGTGGCCCCAACACACGGATCATTGCCACTACCAAGGGCGAGTAAGGGGCTTCCCCG
 ACTCCTGGGTAGTCTCTGCACTGCTCTGGGATGAGTGGCCTGATCACCTCAGCAGGAATGCCAGCTATTATC
 TGGCTCCCTGGCCACCCCGGGGCTCCAAGGACTTCTCAACCCACGAGATCTTTCGGATGGAGCAGCTGCTCACCT
 GGAAAGGAACCTGTGGCCACAGGGATCCTGGGAACAAAGCGGGCATGACCAGCCTTCTGGTGGTCCCAGAGCA
 GGGCAGGCGAGAAGCGCGCAGGACCCGGAAGTACCTGGAAGTGTACATTGTGGCAGACCACACCCTGTTCTTGA
 CTCGGCACCGAAACTTGAACACACCAAACAGCGTCTCCTGGAAGTCGCCAACTACGTGGACCAGCTTCTCAGGA
 CTCTGGACATTAGGTGGCGCTGACCGGCTGGAGGTGTGGACCGAGCGGGACCGCAGCCGCGTCACGCAGGACG
 CCAACGCCACGCTCTGGGCCTTCTGCACTGGCGCCGGGGGCTGTGGGCGCAGCGGCCCCACGACTCCGCGCAGC
 TGCTACGGGCGCGCCTTCCAGGGCGCCACAGTGGGCCTGGCGCCCGTCGAGGGCATGTGCCGCGCCGAGAGCT
 CGGGAGGCGTGAGCACGGACCACTCGGAGCTCCCATCGGCGCCGACGCCACCATGGCCCATGAGATCGGCCACA
 GCCTCGGCCTCAGCCACGACCCCGACGGCTGCTGCGTGGAGGCTGCGGCCGAGTCCGGAGGCTGCGTCATGGCTG
 CGGCCACCGGGCACCCGTTTCCGCGCGTGTTCAGCGCTGACGCCCGCCGAGCTGCGCGCCTTCTCCGCAAGG
 GGGGCGGCGCTTGCCTCTCCAATGCCCCGACCCCGGACTCCCGGTGCCGCCGCGCTCTGCGGGAACGGCTTCG
 TGGAAGCGGGCGAGGAGTGTGACTGCGGCCCTGGCCAGGAGTGC CGCGACCTCTGCTGCTTTGCTCACAACCTGCT
 CGCTGCGCCCGGGGGCCAGTGC GCCCACGGGACTGCTGCGTGCGCTGCTGCTGCTGAAGCCGGCTGGAGCGCTGT
 GCCGCCAGGCCATGGGTGACTGTGACCTCCCTGAGTTTGCACGGGCACCTCCTCCCACTGTCCCCCAGACGTTT
 ACCTACTGGACGGCTCACCTGTGCCAAGGGCAGTGGCTACTGCTGGGATGGCGCATGTCCCAGCTGGAGCAGC
 AGTGCCAGCAGCTCTGGGGGCTGGCTCCCAACCCAGCTCCCGAGGCTGTTTCCAGGTGGTGAACCTCTGCGGGAG
 ATGCTCATGGAACTGCGGCCAGGACAGCGAGGGCCACTTCTGCCCTGTGCAGGGAGGGATGCCCTGTGTGGGA
 AGCTGCAGTGCCAGGTGGAAAGCCAGCCTGCTGCGACCGCACATGGTGCCAGTGGACTCTACCGTTACCTAG
 ATGGCCAGGAAGTGACTTGTGCGGGAGCCTTGGCACTCCCCAGTGGCCAGCTGGACCTGCTTGGCCTGGGCCTGG
 TAGAGCCAGGCACCCAGTGTGGACCTAGAATGGTGTGCCAGAGCAGGCGCTGCAGGAAGAATGCCTTCCAGGAGC
 TTCAGCGCTGCCCTGACTGCTGCCACAGCCACGGGGTTTGAATAGCAACCATAACTGCCACTGTGCTCCAGGCT
 GGGCTCCACCCTTCTGTGACAAGCCAGGCTTGGTGGCAGCATGGACAGTGGCCCTGTGCAGGCTGAAAACCATG
 ACACCTTCTGCTGGCCATGCTCCTCAGCGTCTGCTGCTGCTGCTCCAGGCGCCGGCCTGGCCTGGTGTGCT
 ACCGACTCCCAGGAGCCCATCTGCAGCGATGCAGCTGGGGCTGCAGAAGGGACCTGCGTGCAGTGGCCCCAAG
 ATGGCCACACAGAGACCACCCCTGGGCGCGTTTACCCCATGGAGTTGGGCCCCACAGCCACTGGACAGCCCT
 GGCCCTTGGACCCTGAGAACTCTCATGAGCCAGCAGCCACCCTGAGAAGCCTCTGCCAGCAGTCTCGCCTGACC
 CCAAGCAGATCAAGTCCAGATGCCAAGATCCTGCCTCTGTGGCGAACCCTGGGGAGGCCACGTGGGAAGGAAAG
 AGGGCTCTAAGAGGGGAGGCCCCAGACTGGGGGAGAGGCTGTCTGGAGCCAGGATCACCTGGCTGTGCTGCAG
 AACTGGAGAAGAGAAGCTCAGCAGAAAGGAGCTGGCATGGGGCCAACAGCAGAAAAGCAGGAGGCACGCAGAAGT
 GACTGGGAAGCAGGA
 GG

The sequence of NOV7c was derived by laboratory cloning of cDNA fragments, by *in*
silico prediction of the sequence. The cDNA fragments covering either the full length of the DNA
 sequence, or part of the sequence, or both, were cloned. *In silico* prediction was based on
 sequences available in CuraGen's proprietary sequence databases or in the public human
 sequence databases, and provided either the full length DNA sequence, or some portion thereof.

The DNA sequence and protein sequence for a novel stabilin-like gene were obtained by
 SeqCalling™ Technology and are reported here as NOV7c. These methods used to amplify
 NOV7c cDNA are described in Example 2.

The NOV7c polypeptide (SEQ ID NO:26) encoded by SEQ ID NO:25 is 874 amino acid residues in length and is presented using the one-letter amino acid code in Table 7F. The SignalP, Psort and/or Hydropathy results predict that NOV7c has a signal peptide and is likely to be localized extracellularly at the plasma membrane with a certainty of 0.4600. In alternative

5 embodiments, a NOV7c polypeptide is located to the microbody (peroxisome) with a certainty of 0.1000, the endoplasmic reticulum (membrane) with a certainty of 0.1000, or the endoplasmic reticulum (lumen) with a certainty of 0.1000. The SignalP predicts a likely cleavage site for a NOV7c peptide between amino acid positions 29 and 30, i.e. at the dash in the sequence GAG-VL.

Table 7F. Encoded NOV7b Protein Sequence (SEQ ID NO:26)

MGWRPRRARGTPLL LLLLLLLLLLWFPVPGAGVLQGHIPGQPVTPHWVLDGQPWRTVSLEEPVSKPDMGLVALEAEGQE
 L LLELEKHNHRL LAPGYIETHYGPDPVVLAPNHTDHCHYQGRVRGFPDSWVVLCTCSGMSGLITLSRNASYLRLP
 WPPRGSKDFSTHEIFRMEQLLTWKGTGHRDPGNKAGMTSLPGGPQSRGRREARRTRKYLELYIVADHTLFLTRHR
 NLNHTKQRLLEVANYVDQLLRTLDIQVALTGLEVWTERDRSRVTQDANATLWAFLOWRRGLWAQRPDHAQLLTGR
 AFQGATVGLAPVEGMCRAESSGGVSTDHSELP I GAAATMAHEIGHSLGLSHDPDGCCVEAAAESGGCVMAAATGHP
 FPRVFSACSRRLRAFFRKGGGACLSNAPDPGLPVPPALCGNGFVEAGEECDGPGQECRDLCFAHNCSLRPGAQ
 CAHGDCCVRCLLKPA GALCRQAMGDCDLPEFCTGTSSHCPD VYLLDGSPCAKSGSYCWDGACPTLEQQCQQLWGP
 GSHPAPEACFQVVNSAGDAHNGCGQDSEGHFLPCAGRDALCGKLQCQGGKPSLLAPHMVVDSTVHLDGQEVTCRG
 ALALPSAQLDLLGLGLVEPGTQCGPRMVCQSRRCRKNAFQELQRC LTACHSHGVCNSNHNCHCAPGWAPPFCDKPG
 FGGSMDSGPVQAENHDTFLLAMLLSVLLPLLPGAGLAWCCYRLPGAHLQRC SWGCRRDPACSGPKDGPDRDHPLGG
 VHPMELGPTATGQWPWLPDPENSHEPSSHPEKPLPAVSPDPQADQVQMPRSLCCEPWGGHVGRKEGSKRGGPRLGE
 RPVWSPGSPGCAAELEKRSSAERSWHGANSRKAGGTQK

SNP variants of NOV7 are disclosed in Example 3.

NOV7 Clones

15 Unless specifically addressed as NOV7a, NOV7b, or NOV7c, any reference to NOV7 is assumed to encompass all variants.

The amino acid sequence of NOV7 has high homology to other proteins as shown in Table 7G.

Table 7G. BLASTX Results from Patp Database for NOV7

Sequences Producing High-Scoring Segment Pairs:		High Score	Smallest Sum Prob P (N)
patp:AAB47106	Second splice variant of MAPP - Homo sapiens	4372	0.0
patp:AAB47105	First splice variant of MAPP - Homo sapiens	3666	0.0

patp:AAB50935	ADAM protein #1 - Homo sapiens	1790	1.6e-188
patp:AAB50942	ADAM gene #1 peptide #1 - Homo sapiens	1790	6.6e-186
patp:AAW25716	Mouse beta meltrin protein	1753	2.1e-180

In a search of sequence databases, it was found, for example, that the NOV7a nucleic acid sequence of this invention has 811 of 840 bases (96%) identical to a gb:GENBANK-

- 5 ID:HSM801104|acc:AL117415.1 mRNA from Homo sapiens (Homo sapiens mRNA; cDNA DKFZp434K0521 (from clone DKFZp434K0521)). Further, the full amino acid sequence of the disclosed NOV7a protein of the invention has 553 of 554 amino acid residues (99%) identical to, and 553 of 554 amino acid residues (99%) similar to, the 702 amino acid residue
 10 ptrn:TREMBLNEW-ACC:CAC16509 protein from Homo sapiens (Human) (DJ964F7.1 (NOVEL PROTEIN (DISINTEGRIN AND METALLOPROTEINASE))).

- In a similar search of sequence databases, it was found, for example, that the NOV7b and NOV7c nucleic acid sequences have 1409 of 2252 bases (62%) identical to a gb:GENBANK-
 15 ID:XLU66003|acc:U66003.1 mRNA from Xenopus laevis (Xenopus laevis ADAM 13 mRNA, complete cds). Further, the full amino acid sequence of the disclosed NOV7b and NOV7c proteins of the invention have 388 of 746 amino acid residues (52%) identical to, and 507 of 746 amino acid residues (67%) similar to, the 914 amino acid residue ptrn:SPTREMBL-ACC:O12960 protein from Xenopus laevis (African clawed frog) (ADAM 13).

Additional BLASTP results are shown in Table 7H.

Table 7H. NOV7 BLASTP Results

Gene Index/ Identifier	Protein/Organism	Length of aa	Identity (%)	Positives (%)	Expect Value
CAC33154	SEQUENCE 3 FROM PATENT WO0109293 - Homo sapiens (Human)	812	785/811 (96%)	789/811 (97%)	0.0
Q9BZ11	DJ964F7.1 (NOVEL DISINTEGRIN AND REPROLYSIN METALLOPROTEINASE FAMILY PROTEIN) - Homo sapiens (Human)	728	699/716 (97%)	701/716 (97%)	0.0
CAC33153	SEQUENCE 1 FROM PATENT WO0109293 - Homo sapiens (Human)	802	661/661 (100%)	661/661 (100%)	0.0
AAK67164	ADAM33 - Mus musculus	685	498/690	543/690	3.8e-280

	(Mouse)		(72%)	(78%)	
O12960	ADAM 13 - <i>Xenopus laevis</i> (African clawed frog)	914	388/746 (52%)	507/746 (67%)	9.4e-211

A multiple sequence alignment is given in Table 7I, with the NOV7 protein of the invention being shown in lines 1, 2, and 3 in a ClustalW analysis comparing NOV7 with related protein sequences of Table 7H.

Table 7I. ClustalW Analysis of NOV7

1. SEQ ID NO.: 22	NOV7a	5. SEQ ID NO.: 80	Q9BZ11
2. SEQ ID NO.: 24	NOV7b	6. SEQ ID NO.: 81	CAC33153
3. SEQ ID NO.: 26	NOV7c	7. SEQ ID NO.: 82	AAK67164
4. SEQ ID NO.: 79	CAC33154	8. SEQ ID NO.: 83	O12960

15	NOV7a	MGWRPRRRARGTPLLILLILLILLWPVPGAGVLQGHIPGQPVTTPHWVLDGQPWRTVSLEEPV	60
	NOV7b	MGWRPRRRARGTPLLILLILLILLWPVPGAGVLQGHIPGQPVTTPHWVLDGQPWRTVSLEEPV	60
	NOV7c	MGWRPRRRARGTPLLILLILLILLWPVPGAGVLQGHIPGQPVTTPHWVLDGQPWRTVSLEEPV	60
	CAC33154	MGWRPRRRARGTPLLILLILLILLWPVPGAGVLQGHIPGQPVTTPHWVLDGQPWRTVSLEEPV	60
	Q9BZ11	-----	1
	CAC33153	MGWRPRRRARGTPLLILLILLILLWPVPGAGVLQGHIPGQPVTTPHWVLDGQPWRTVSLEEPV	60
20	AAK67164	-----	1
	O12960	MGTEGRLSTWLGLGAVIVGLLIPVLTLCAGQC---ELVTAFWLQNGRAKESVDLLDKG	56
25	NOV7a	SKPDMGLVALEAEGQELLLELEKHNHRLAPGYIETHYGPDPQPVVLAPNHTDHCHYQGRV	120
	NOV7b	SKPDMGLVALEAEGQELLLELEKHNHRLAPGYIETHYGPDPQPVVLAPNHTDHCHYQGRV	120
	NOV7c	SKPDMGLVALEAEGQELLLELEKHNHRLAPGYIETHYGPDPQPVVLAPNHTDHCHYQGRV	120
	CAC33154	SKPDMGLVALEAEGQELLLELEKHNHRLAPGYIETHYGPDPQPVVLAPNHTDHCHYQGRV	120
	Q9BZ11	-----RLLAPGYIETHYGPDPQPVVLAPNHTDHCHYQGRV	35
	CAC33153	SKPDMGLVALEAEGQELLLELEKHNHRLAPGYIETHYGPDPQPVVLAPNHTDHCHYQGRV	120
30	AAK67164	-----DHCQYHGRV	9
	O12960	-TPDGGETLVSSSEGRKFTLLKVERNHLLFAPGYTETHY-TDGMVTLSPNHTDHCHYHGV	114
35	NOV7a	RGFPDSWVVLCTCSGMSGLITLSRNASYLLRPWPPRGSKDFSTHEIFRMEQLLTWKGTCC	180
	NOV7b	RGFPDSWVVLCTCSGMSGLITLSRNASYLLRPWPPRGSKDFSTHEIFRMEQLLTWKGTCC	180
	NOV7c	RGFPDSWVVLCTCSGMSGLITLSRNASYLLRPWPPRGSKDFSTHEIFRMEQLLTWKGTCC	180
	CAC33154	RGFPDSWVVLCTCSGMSGLITLSRNASYLLRPWPPRGSKDFSTHEIFRMEQLLTWKGTCC	180
	Q9BZ11	RGFPDSWVVLCTCSGMSGLITLSRNASYLLRPWPPRGSKDFSTHEIFRMEQLLTWKGTCC	95
	CAC33153	RGFPDSWVVLCTCSGMSGLITLSRNASYLLRPWPPRGSKDFSTHEIFRMEQLLTWKGTCC	180
	AAK67164	RGFRESWVVLSTCSGMSGLIVLSSKVSYYLOPRTPGDTKDFSTHEIFRMEQLFTWRGVQR	69
40	O12960	ENYDESSVALITCSGISGLIWLSTNNSYYLKPLEVPCKE---THILVRLTEHLIKEGSCG	171
45	NOV7a	HR-DPGNKAG---MTSLPGGPQSRGRREARRTRKYLELYIVADHTLFLTRHRNLNHTKQR	236
	NOV7b	HR-DPGNKAG---MTSLPGGPQSRGRREARRTRKYLELYIVADHTLFLTRHRNLNHTKQR	236
	NOV7c	HR-DPGNKAG---MTSLPGGPQSRGRREARRTRKYLELYIVADHTLFLTRHRNLNHTKQR	236
	CAC33154	HR-DPGNKAG---MTSLPGGPQSRGRREARRTRKYLELYIVADHTLFLTRHRNLNHTKQR	236
	Q9BZ11	HR-DPGNKAG---MTSLPGGPQSRGRREARRTRKYLELYIVADHTLFLTRHRNLNHTKQR	151
	CAC33153	HR-DPGNKAG---MTSLPGGPQSRGRREARRTRKYLELYIVADHTLFLTRHRNLNHTKQR	236
	AAK67164	DK-NSQYKAG---MASLPHVPSQSRVRREARRSPRYLELYIVADHTLFLLOHONLNHTRQR	125
	O12960	HDGHSGLTASYLQEFAPSSHHHRVRRNVWRSSQKYMELFIVADYSMEFMKONRNLGSTKQR	231

5	NOV7a	LLEVANYVDQLLRITLDIQVALTGLEVWTERDRSRVTQDANATLWAFLOWRRGLWAQRPHD	296
	NOV7b	LLEVANYVDQLLRITLDIQVALTGLEVWTERDRSRVTQDANATLWAFLOWRRGLWAQRPHD	296
	NOV7c	LLEVANYVDQLLRITLDIQVALTGLEVWTERDRSRVTQDANATLWAFLOWRRGLWAQRPHD	296
	CAC33154	LLEVANYVDQLLRITLDIQVALTGLEVWTERDRSRVTQDANATLWAFLOWRRGLWAQRPHD	296
	Q9BZ11	LLEVANYVDQLLRITLDIQVALTGLEVWTERDRSRVTQDANATLWAFLOWRRGLWAQRPHD	211
	CAC33153	LLEVANYVDQLLRITLDIQVALTGLEVWTERDRSRVTQDANATLWAFLOWRRGLWAQRPHD	296
10	AAK67164	LLEVANCVDQLLRITLDIQVLVTGLEVWTEQDLISRTQDANETLWAFLOWRRGVWARRPHD	185
	O12960	VLEIANVVDKFYMSMNIRKVALIGLEVWTERDQCEVNDANDSLKSFLOWKQKLRSRKKHD	291
15	NOV7a	SAQLLTGRAFOGATVGLAPVEGMCRAESSGGVSTDHSELPIGAAATMAHEIGHSLGLSH	355
	NOV7b	SAQLLTGRAFOGATVGLAPVEGMCRAESSGGVSTDHSELPIGAAATMAHEIGHSLGLSH	355
	NOV7c	SAQLLTGRAFOGATVGLAPVEGMCRAESSGGVSTDHSELPIGAAATMAHEIGHSLGLSH	355
	CAC33154	SAQLLTGRAFOGATVGLAPVEGMCRAESSGGVSTDHSELPIGAAATMAHEIGHSLGLSH	355
	Q9BZ11	SAQLLTGRAFOGATVGLAPVEGMCRAESSGGVSTDHSELPIGAAATMAHEIGHSLGLSH	270
	CAC33153	SAQLLTGRAFOGATVGLAPVEGMCRAESSGGVSTDHSELPIGAAATMAHEIGHSLGLSH	355
20	AAK67164	STQLLTGRITFOGTTVGLAPVEDMPRGELSGGVSTDHSELPIGTAATMAHEIGHSLGLHH	245
	O12960	NAQLITGVTEKGTITIGMAPLEGMCCTAENS-GGVSMHSENAIGAAATMAHEIGHNFGMSH	350
25	NOV7a	DPDGCCVEAAAESGGCVMAAATGHPFPRVFSACSRRLRAFFRKGGGACLSNAPDPGLPV	415
	NOV7b	DPDGCCVEAAAESGGCVMAAATGHPFPRVFSACSRRLRAFFRKGGGACLSNAPDPGLPV	415
	NOV7c	DPDGCCVEAAAESGGCVMAAATGHPFPRVFSACSRRLRAFFRKGGGACLSNAPDPGLPV	415
	CAC33154	DPDGCCVEAAAESGGCVMAAATGHPFPRVFSACSRRLRAFFRKGGGACLSNAPDPGLPV	415
	Q9BZ11	DPDGCCVEAAAESGGCVMAAATGHPFPRVFSACSRRLRAFFRKGGGACLSNAPDPGLPV	330
	CAC33153	DPDGCCVEAAAESGGCVMAAATGHPFPRVFSACSRRLRAFFRKGGGACLSNAPDPGLPV	415
30	AAK67164	DPEGCCVQADAEQGGCVMAAATGHPFPRVFSACSRRLRAFFRKGGGACLSNAPDPGLPV	305
	O12960	D-DGCCVEATPEQGGCMAAATGHPFPRKFFSSCSQKOLMSYFQKGGGMCLFNMENTKDLV	409
35	NOV7a	PPALCGNGFVEAGEECDGPGQECRDLCCFAHNCSLRPGAQCAHGDCCVRCLLKPGALC	475
	NOV7b	PPALCGNGFVEAGEECDGPGQECRDLCCFAHNCSLRPGAQCAHGDCCVRCLLKPGALC	475
	NOV7c	PPALCGNGFVEAGEECDGPGQECRDLCCFAHNCSLRPGAQCAHGDCCVRCLLKPGALC	475
	CAC33154	PPALCGNGFVEAGEECDGPGQECRDLCCFAHNCSLRPGAQCAHGDCCVRCLLKPGALC	475
	Q9BZ11	PPALCGNGFVEAGEECDGPGQECRDLCCFAHNCSLRPGAQCAHGDCCVRCLLKPGALC	390
	CAC33153	PPALCGNGFVEAGEECDGPGQECRDLCCFAHNCSLRPGAQCAHGDCCVRCLLKPGALC	475
40	AAK67164	LPSRCNGNGLFVEAGEECDGSGQKCPDPCCFAHNCSLRAGAQCAHGDCCARCLLKSAQTQC	365
	O12960	MGKKCCNGNGLFVEAGEECDGCGEPEECTNSCCNANNCTLKAGAQCAHGECCQDCKLKSAGTQC	469
45	NOV7a	RQAMGDCDLPEFCTGTSSHCPPDVYLLDGSPCARSGSGYCWGDGACPTLEQQCQQLWGPESH	535
	NOV7b	RQAMGDCDLPEFCTGTSSHCPPDVYLLDGSPCARSGSGYCWGDGACPTLEQQCQQLWGPESH	535
	NOV7c	RQAMGDCDLPEFCTGTSSHCPPDVYLLDGSPCARSGSGYCWGDGACPTLEQQCQQLWGPESH	535
	CAC33154	RQAMGDCDLPEFCTGTSSHCPPDVYLLDGSPCARSGSGYCWGDGACPTLEQQCQQLWGPESH	535
	Q9BZ11	RQAMGDCDLPEFCTGTSSHCPPDVYLLDGSPCARSGSGYCWGDGACPTLEQQCQQLWGPESH	450
	CAC33153	RQAMGDCDLPEFCTGTSSHCPPDVYLLDGSPCARSGSGYCWGDGACPTLEQQCQQLWGPESH	535
50	AAK67164	RPAATDCDLPEFCTGTSPYCPADVYLLDGSPCAEGRGYCLDGWCPTLEQQCQQLWGPESH	425
	O12960	REMAGSCDLPEFCTGTGAPSCPSNVYKLDGSLCADGNAYCYNMCLTHQCCQCIHLWGSQAV	529
55	NOV7a	PAPEACFQVNSAGDAHGNCQDSEGHFLPCAGRDALCGKLQCGGKPSLLAPHMVPVDS	595
	NOV7b	PAPEACFQVNSAGDAHGNCQDSEGHFLPCAGRDALCGKLQCGGKPSLLAPHMVPVDS	595
	NOV7c	PAPEACFQVNSAGDAHGNCQDSEGHFLPCAGRDALCGKLQCGGKPSLLAPHMVPVDS	595
	CAC33154	PAPEACFQVNSAGDAHGNCQDSEGHFLPCAGRDALCGKLQCGGKPSLLAPHMVPVDS	595
	Q9BZ11	PAPEACFQVNSAGDAHGNCQDSEGHFLPCAGRDALCGKLQCGGKPSLLAPHMVPVDS	510
	CAC33153	PAPEACFQVNSAGDAHGNCQDSEGHFLPCAGRDALCGKLQCGGKPSLLAPHMVPVDS	595
55	AAK67164	PAPEPCFOQMSMCMNSQGNCCQDHEKGSFLPCAQRDALCGKLQCGGEPNPLVPHIVTMDS	485
	O12960	VAPNFCFQDVNKAQDOYGNCCGNRGQFVKCTSRDAKCKGIQCQTSSEKPRDPSMVKVDN	589
55	NOV7a	TVHLDGQEVTCRGALALPSAQLDLLGLGLVEPGTQCGPRMVCQSRRCKRNAFQELQRCIT	655
	NOV7b	TVHLDGQEVTCRGALALPSAQLDLLGLGLVEPGTQCGPRMVCQSRRCKRNAFQELQRCIT	655
	NOV7c	TVHLDGQEVTCRGALALPSAQLDLLGLGLVEPGTQCGPRMVCQSRRCKRNAFQELQRCIT	655

	CAC33154	TVHLDGQEVTCRGALALPSAQLDLLGLGLVEPGTQCGPRMVCQSRRCRKNAFQELQRC	655
	Q9BZ11	TVHLDGQEVTCRGALALPSAQLDLLGLGLVEPGTQCGPRMVCQSRRCRKNAFQELQRC	570
	CAC33153	TVHLDGQEVTCRGALALPSAQLDLLGLGLVEPGTQCGPRMVCQSRRCRKNAFQELQRC	655
	AAK67164	TTLEEGREVVCRGAFVLPDSHLDQLDLGLVEPGTQCGPRMVCQDRHCQONATSQELERCLT	545
5	O12960	TTITNGYKMKQCGVHAY-SMOEEEGDPGLVMTGTRKCGDGMVCKDRRCQNASFFELDQC	648
	NOV7a	ACHSHGVCNSNHNCHCAPGWAPPFCDKPGFGGSMDSGPVQAEHDTFLLAMLLSVLLPLL	715
	NOV7b	ACHSHGVCNSNHNCHCAPGWAPPFCDKPGFGGSMDSGPVQAEHDTFLLAMLLSVLLPLL	715
	NOV7c	ACHSHGVCNSNHNCHCAPGWAPPFCDKPGFGGSMDSGPVQAEHDTFLLAMLLSVLLPLL	715
10	CAC33154	ACHSHGVCNSNHNCHCAPGWAPPFCDKPGFGGSMDSGPVQAEHDTFLLAMLLSVLLPLL	715
	Q9BZ11	ACHSHGVCNSNHNCHCAPGWAPPFCDKPGFGGSMDSGPVQAEHDTFLLAMLLSVLLPLL	630
	CAC33153	ACHSHG-----ACLHPSVTSQALVAA--WTVALCRLKTMTPSCW	692
	AAK67164	ACHNCGVCNSNRNCHCAAGWAPPFCDKPGFGGSVDSGPAQSANRDAFPLAMLLSFLLPLL	605
	O12960	KCNCHGVCNSNRNCHCDSGWAPPFCDKPGFGGSQDSGPAPSDLPVGVTTFLLVLLFLVLL	708
15	NOV7a	PGAGLAWCCYRLPGAHLQRCSWGCR-----DPACSGP	748
	NOV7b	PGAGLAWCCYRLPGAHLQRCSWGCR-----DPACSGP	748
	NOV7c	PGAGLAWCCYRLPGAHLQRCSWGCR-----DPACSGP	748
	CAC33154	PGAGLAWCCYRLPGAHLQRCSWGCR-----DPACSGP	748
20	Q9BZ11	PGAGLAWCCYRLPGAHLQRCSWGCR-----DPACSGP	663
	CAC33153	P-CSSASCCLCSQGPAPWPGVATDSQ-----EPICSDA	723
	AAK67164	PGAGLAWCYQLP--TFCHRRGLCCRR-----DPLWN--	634
	O12960	ALAFAMVYWYRKPGSLNRLWLMKSKAKCSLCKATQPKANRAYSSRIFTLRNISYPVKSTS	768
25	NOV7a	KDGPHRDHPLGGVHPMELGPTATGQPWPLDPGAPADHIHNIYPPPFLLDPENSHEPSSHP	808
	NOV7b	KDGPHRDHPLGGVHPMELGPTATGQPWPLDP-----ENSHEPSSHP	789
	NOV7c	KDGPHRDHPLGGVHPMELGPTATGQPWPLDP-----ENSHEPSSHP	789
	CAC33154	KDGPHRDHPLGGVHPMELGPTATGQPWPLDP-----ENSHEPSSHP	789
	Q9BZ11	KDGPHRDHPLGGVHPMELGPTATGQPWPLDP-----ENSHEPSSHP	704
30	CAC33153	AG--AAEGTLRAVAPKMAHTGTT--PWAAFT-----PWSWA	755
	AAK67164	-----RDIPLGSVHPVEFGSIITGEPSPPPP-----WTISC	664
	O12960	KETRSRDIFQGKTTAAQNSSQPVNVVRPLRP-----APSPVIOHGVO	810
35	NOV7a	EKPLPAVSPDPQGGSLAAWGSPPLGDNISSSFSADQVQMPRSCLCGEPW-GGHVGRKEGS	867
	NOV7b	EKPLPAVSPDPQGGSLAAWGSPPLGDNISSSFSADQVQMPRSCLCGEPW-GGHVGRKEGS	848
	NOV7c	EKPLPAVSPDPQ-----ADQVQMPRSCLCGEPW-GGHVGRKEGS	827
	CAC33154	EKPLPAVSPDPQ-----DQVQMPRSCW-----	812
	Q9BZ11	EKPLPAVSPDPQ-----ADQVQMPRSCW-----	728
	CAC33153	PPPLDSPGPWTLR-----TLMSPAATLRSLCQ-QSRITPKIKS	792
40	AAK67164	QQRSHPPSLDLLS-----DPANSELT-----	685
	O12960	VKPLRPPPPPMKPSPILP-----AKEQTVHVKLILPKKPLPSCPIRTOQLNPPSKP	861
	NOV7a	KRGGPERLGERPVWSPGSPGCAAELEKRSSAERSWHGANSRKAGGTQK-----	914
	NOV7b	KRGGPERLGERPVWSPGSPGCAAELEKRSSAERSWHGANSRKAGGTQK-----	895
45	NOV7c	KRGGPERLGERPVWSPGSPGCAAELEKRSSAERSWHGANSRKAGGTQK-----	874
	CAC33154	-----	812
	Q9BZ11	-----	728
	CAC33153	RCQDPASGER-----	802
	AAK67164	-----	685
50	O12960	LPVTEPAHKEPLLVLTPATHKPPITNSATQLKGPHRPIQGGKVQAAAAAFLQK	914

Domain results for NOV7 were collected from the Pfam database, and then identified by the Interpro domain accession number. The results are listed in Table 7J with the statistics and

domain description. These results indicate that the NOV7 polypeptides have properties similar to those of other proteins known to contain these domains.

Table 7J. Domain Analysis of NOV7

PSSMs Producing Significant Alignments		Score (bits)	E Value
Reprolysin (M12B) family zinc metalloprotease: domain 1 of 1, from 210 to 409		306.6	3.1e-88
Reprolysin	kYiELvIVvDhgmytkygsdlnkirqrVhqivNlvNeiYrpqLNirV + + + + + ++ ++++++ +++++ +++ +++ +		
NOV7a	KYLELYIVADHTLFLTRHRNLNHTKQRLLEVANYVDQLLRT-LDIQV		
NOV7a	vLvGLEIWsdgDkInvqsandTLhsFgeWRetdLlkrksHDnAqLLtgi + ++ + +++ + ++++++ ++ + +++ + +++ ALTGLEVWTERDRSRVTQDANATLWAFLOWRRG-LWAQRPHDSAQLLTGR		
NOV7a	dfdgnTiGaAyvggmCspkrSvGVvqdhspivllvAvtMAHELGHNLGmt +++ ++ + ++ ++ +++ + +++++ +++ ++ + + + + AFQGATVGLAPVEGMCRAESSGGVSTDHSELPIGAAATMAHEIGHSLGLS		
NOV7a	HDdknkdGcTcCe...gggsCIMnpvasspskKkFSnCSkddyqkFltkq ++ + + + +++++ + +++++ + + +++ ++ HDPD---GCCVEaaaESGGCVMAAATGHPFPR-VFSACSRRLRAFFRKG		
NOV7a	kpqCLlNkP (SEQ ID NO:84) +++ + GGACLSNAP (SEQ ID NO:22)		
Pep_M12B_propep (Reprolysin family propeptide): domain 1 of 1, from 80 to 198		112.3	9e-30
M12B Propep	hLeknrslapdfvtvttYdedGtlvteepli qddHCyYqGyVeGypn +++++ +++++ +++ + +++ +++++ + + + + + +++ ELEKNHRLAPGYIETHYGPDGQPVVLAPNHT-DHCHYQGRVRGFPD		
NOV7a	SaVslSTCsGgLRGIlqlenlsYgIEPle..ssdgf.eHiiYqiendkte + ++ + +++ + + ++ +++++ +++++ ++++++ + SWVVLCTCSGMSGLITLSRNASYLRPWpPrGSKDFsTHEIFRMEQLLTW		
NOV7a	pspcgecgslststdssygirsasp (SEQ ID NO:85) +++++ + + + + + + KGTGCHRD PGN-KAGMTSLPGGPQ (SEQ ID NO:22)		

5

The NOV7 disclosed in this invention is expressed in at least the following tissues:
Ascending Colon, Cervix, Heart, Liver, Lymph node, Mammary gland/Breast, Ovary, Peripheral Blood, Placenta, Retina, Skin, Stomach, Testis, Uterus, and Whole Organism. This information

was derived by determining the tissue sources of the sequences that were included in the invention including but not limited to SeqCalling sources, Public EST sources, Literature sources, and/or RACE sources.

5 The protein similarity information, expression pattern, and map location for the ADAM13-like protein and nucleic acid disclosed herein suggest that this protein may have important structural and/or physiological functions characteristic of the ADAM protein family. Therefore, the nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications and as a research tool. For example, the compositions of the present invention will have efficacy for treatment of patients suffering from: Xerostomia, Scleroderma, Hypercalceimia, 10 Ulcers, Von Hippel-Lindau (VHL) syndrome, Cirrhosis, Transplantation, Cirrhosis, Inflammatory bowel disease, Diverticular disease, Hirschsprung's disease, Crohn's Disease, Appendicitis, Endometriosis, Fertility, Cardiomyopathy, Atherosclerosis, Hypertension, Congenital heart defects, Aortic stenosis, Atrial septal defect (ASD), Atrioventricular (A-V) canal defect, Ductus arteriosus, Pulmonary stenosis, Subaortic stenosis, Ventricular septal defect (VSD), valve 15 diseases, Tuberous sclerosis, Scleroderma, Obesity, Aneurysm, Fibromuscular dysplasia, Stroke, Bleeding disorders, Hemophilia, hypercoagulation, Idiopathic thrombocytopenic purpura, autoimmune disease, allergies, immunodeficiencies, Graft versus host, Anemia, Ataxia-telangiectasia, Lymphedema, Allergies, and Tonsillitis and other diseases, disorders and conditions of the like.

20 The novel nucleic acid encoding the ADAM13-like protein of the invention, or fragments thereof, are useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed. These materials are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, 25 using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. The disclosed NOV7 protein has multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, a contemplated NOV7 epitope is from about amino acids 40 to 60. In another embodiment, a contemplated NOV7 epitope is from about amino acids 70 to 125. In alternative embodiments, contemplated NOV7 epitopes include from 30 about amino acids 140 to 210, 220 to 250, 260 to 310, 320 to 360, 370 to 410, 420 to 460, 470 to 610, 620 to 700, and 710 to 910.

NOV8

Yet a further NOVX protein of the invention, referred to herein as NOV8 (alternatively referred to as CG50321-01), is a leucine-rich repeat containing an F-box protein-like protein.

F-box proteins are an expanding family of eukaryotic proteins characterized by an approximately 40 amino acid motif, the F box (so named because cyclin F was one of the first proteins in which this motif was identified). Some F-box proteins are known to be critical for the controlled degradation of cellular regulatory proteins. In fact, F-box proteins are one of the four subunits of ubiquitin protein ligases called SCFs. SCF ligases bring ubiquitin conjugating enzymes (either Ubc3 or Ubc4) to substrates that are specifically recruited by the different F-box proteins. The need for high substrate specificity and the large number of known F-box proteins in yeast and worms suggest the existence of a large family of mammalian F-box proteins. Some of these proteins contain WD-40 domains or leucine-rich repeats; others contain either different protein-protein interaction modules or no recognizable motifs. They named the F-box proteins that contain WD-40 domains Fbws, those containing leucine-rich repeats, Fbls, and the remaining ones Fbxs. The marked differences in F-box gene expression in human tissues is exemplar of their distinct role in ubiquitin-dependent protein degradation.

The NOV8 protein predicted here is localized extracellularly at the plasma membrane. Therefore, it is likely that this leucine-rich containing F-box protein-like protein is accessible to a diagnostic probe, and for the various therapeutic applications described herein.

The NOV8 protein disclosed in this invention maps to chromosome 17. This information was assigned using OMIM, the electronic northern bioinformatic tool implemented by CuraGen Corporation, public ESTs, public literature references and/or genomic clone homologies.

The NOV8 nucleic acid (SEQ ID NO:27) of 1307 nucleotides encodes a novel leucine-rich containing F-box protein-like protein and is shown in Table 8A. An open reading frame for the mature protein was identified beginning with a ATG initiation codon at nucleotides 17-19 and ending with a TGA codon at nucleotides 1283-1285. Putative untranslated regions upstream from the start codon and downstream from the termination codon are underlined in Table 8A. The start and stop codons are in bold letters.

Table 8A. NOV8 Nucleotide Sequence (SEQ ID NO:27)

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CAAGAGCAGGTTTGTAGATGTTCTCAAATAGTGATGAAGCTGTAATCAATAAAAACTTCCCAAAGAACTCCTGTT
ACGGATATTTTCTTTTCTAGATGTTGTTACCCTGTGCCGCTGTGCTCAGGTCTCCAGGGCCTGGAATGTTCTGGC
TCTGGATGGCAGTAACCTGGCAGCGAATTGACCTATTTGATTTCCAGAGGGATATTGAGGGCCGAGTAGTGGAGAA
TATTTCAAACGATGTGGGGGCTTTTTACGAAAGTTAAGTCTTCGTGGATGTCTTGGAGTGGGAGACAATGCATT
AAGAACCTTTGCACAAAACCTGCAGGAACATTGAAGTACTGAATCTAAATGGGTGTACAAAGACAATAGACGCTAC
ATGTACTAGCCTTAGCAAGTTCTGTTCCAAACTCAGGCACCTTGACTTGGCTTCCTGTACATCAATAACAAACAT
GCCTCTAAAAGCTCTGAGTGAGGGATGTCCACTGTTGGAGCAGTTGAACATTTCTGGTGTGACCAAGTAACCAA
GGATGGCATTCAAGCACTAGTGAGGGGCTGTGGGGGTCTCAAGGCCTTATTCTTAAAAGGCTGCACGCAGCTAGA
AGATGAAGCTCTCAAGTACATAGGTGCACACTGCCCTGAACTGGTGACTTTGAACTTGACAGACTTGCTTGCAAAT
CACAGATGAAGGTCTCATTACTATATGCAGAGGGTGCCATAAGTTACAATCCCTTTGTGCCTCTGGCTGCTCCAA
CATCACAGATGCCATCCTGAATGCTCTAGGTGAGAACTGCCACGGCTTAGAATATTGGAAGTGGCAAGATGTTTC
TCAATTAACAGATGTGGGCTTTACCACTCTAGCCAGGAATTGCCATGAACCTGAAAAGATGGACCTGGAAGAGTG
TGTTGAGATAACAGATAGCACATTAATCCAACTTTCTATACACTGTCCTCGACTTCAAGTATTGAGTCTGTCTCA
CTGTGAGCTGATCACAGATGATGGAATTCGTACCTGGGGAATGGGGCCTGCGCCCATGACCAGCTGGAGGTGAT
TGAGCTGGACAACTGCCCACTAATCACAGATGCATCCCTGGAGCACTTGAAGAGCTGTGCATAGCCTTGAGCGGAT
AGAACTCTATGACTGCCAGCAAATCACACGGGCTGGAATCAAGAGACTCAGGACCCATTTACCCAATATTAAAGT
CCACGCCTACTTCGCACCTGTCACTCCACCCCATCAGTAGGGGGCAGCAGACAGCGCTTCTGCAGATGCTGCAT
CATCCTATGACAATGGAGGTGGTCAACCTTGG

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The sequence of NOV8 was derived by laboratory cloning of cDNA fragments covering the full length and/or part of the DNA sequence of the invention, and/or by *in silico* prediction of the full length and/or part of the DNA sequence of the invention from public human sequence databases.

The cDNA coding for the NOV8 sequence was cloned by the polymerase chain reaction (PCR). PCR primers were designed based on *in silico* predictions of the full length or some portion (one or more exons) of the cDNA/protein sequence of the invention. The DNA sequence and protein sequence for a novel leucine-rich containing F-Box protein-like gene were obtained by exon linking, or SeqCalling™ Technology and are reported here as NOV8. These primers and methods used to amplify NOV8 cDNA are described in Example 2.

The NOV8 polypeptide (SEQ ID NO:28) encoded by SEQ ID NO:27 is 422 amino acid residues in length and is presented using the one-letter amino acid code in Table 8B. The SignalP, Psort and/or Hydropathy results predict that NOV8 has a signal peptide and is likely to be localized extracellularly at the plasma membrane with a certainty of 0.6500. In alternative embodiments, a NOV8 polypeptide is located to the cytoplasm with a certainty of 0.4500, the microbody (peroxisome) with a certainty of 0.3000, or the mitochondrial matrix space with a certainty of 0.1000.

Table 8B. Encoded NOV8 Protein Sequence (SEQ ID NO:28)

MFSNSDEAVINKKLPKELLLRIFSFLDVVTLCRCAQVSRANVLAIDGSNWQRIDLFDFQDIEGRVVENISKRCGGFLRKLSLRGCLGVGDNALRTFAQNCRNIEVLNLNGCTKTIDATCTSLSKFCSKLRHLDLASCT SITNMPLKALSEGCPILLEQLNISWCDQVTKDGIQALVRGCGGLKALFLKGCTQLEDEALKYIGAHCPVLVTNLQTCLOITDEGLITICRGCHKLQSLCASGCSNITDAILNALGQNCPLRLILEVARCSQLTDVGFTTLARNCHELEKMDLEECVQITDSTLIQLSIHCPRLQVLSLSHCELITDDGIRHLGNGACAHDQLEVIELDNCPITDASLEHLKSCHSLERI ELYDCQQITRAGIKRLRTHLPNIKVHAYFAPVTPPPSVGGSRQRFRCCTIIL

SNP variants of NOV8 are disclosed in Example 3.

The amino acid sequence of NOV8 has high homology to other proteins as shown in Table

5 8C.

Table 8C. BLASTX Results from Patp Database for NOV8

Sequences Producing High-Scoring Segment Pairs:		High Score	Smallest Sum Prob P (N)
patp:AAB48290	Human ZF1 protein	1819	2.1e-187
patp:AAB92961	Human protein sequence	1818	2.7e-187
patp:AAB92791	Human protein sequence	1817	3.4e-187
patp:AA Y83090	F-box protein FBP-22 - Homo sapiens	1786	6.5e-184
patp:AA Y02274 A	F-box protein sequence - Homo sapiens	1562	3.6e-160

In a search of sequence databases, it was found, for example, that the NOV8 nucleic acid sequence of this invention has 737 of 801 bases (92%) identical to a gb:GENBANK-

10 ID:AF182443|acc:AF182443.1 mRNA from Rattus norvegicus (Rattus norvegicus F-box protein FBL2 (FBL2) mRNA, complete cds). Further, the full amino acid sequence of the disclosed NOV8 protein of the invention has 328 of 422 amino acid residues (77%) identical to, and 375 of 422 amino acid residues (88%) similar to, the 423 amino acid residue ptmr:SPTREMBL-ACC:Q9UK27 protein from Homo sapiens (Human) (LEUCINE-RICH REPEATS
15 CONTAINING F-BOX PROTEIN FBL3).

Additional BLASTP results are shown in Table 8D.

Table 8D. NOV8 BLASTP Results

Gene Index/ Identifier	Protein/Organism	Length of aa	Identity (%)	Positives (%)	Expect Value
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AAH07557	RIKEN CDNA 2610511F20 GENE - Homo sapiens (Human)	422	420/422 (99%)	420/422 (99%)	2.0e-230
Q9CZV8	2610511F20RIK PROTEIN - Mus musculus (Mouse)	422	416/422 (98%)	417/422 (98%)	1.1e-227
Q9UK27	LEUCINE-RICH REPEATS CONTAINING F-BOX PROTEIN FBL3 - Homo sapiens (Human)	423	328/422 (77%)	375/422 (88%)	1.6e-187
Q9UKA5	F-BOX PROTEIN FBL2 - Homo sapiens (Human)	425	328/422 (77%)	375/422 (88%)	2.7e-187
Q9NVQ8	CDNA FLJ10576 FIS, CLONE NT2RP2003329, WEAKLY SIMILAR TO PUTATIVE ADENYLATE CYCLASE REGULATORY PROTEIN - Homo sapiens (Human)	423	327/422 (77%)	375/422 (88%)	3.4e-187

A multiple sequence alignment is given in Table 8E in a ClustalW analysis comparing NOV8 with related protein sequences disclosed in Table 8D.

Table 8E. ClustalW Analysis of NOV8

- | | | | |
|-------------------|----------|-------------------|--------|
| 1. SEQ ID NO.: 28 | NOV8 | 4. SEQ ID NO.: 88 | Q9UK27 |
| 2. SEQ ID NO.: 86 | AAH07557 | 5. SEQ ID NO.: 89 | Q9UKA5 |
| 3. SEQ ID NO.: 87 | Q9CZV8 | 6. SEQ ID NO.: 90 | Q9NVQ8 |

15	NOV8	---MFSNSDEAVINKKLPKELLRLRIFSFIDVVTLCRCAQVSRAWNVLALDGSNWQRIDLF	57
	AAH07557	---MFSNSDEAVINKKLPKELLRLRIFSFIDVVTLCRCAQVSRAWNVLALDGSNWQRIDLF	57
	Q9CZV8	---MFSNSDEAVINKKLPKELLRLRIFSFIDVVTLCRCAQVSRAWNVLALDGSNWQRIDLF	57
	Q9UK27	--MVFSNNDEGLINKKLPKELLRLRIFSFIDVVTLCRCAQISKAWNILALDGSNWQRIDLF	58
	Q9UKA5	SAMVFSNNDEGLINKKLPKELLRLRIFSFIDVVTLCRCAQISKAWNILALDGSNWQRIDLF	60
	Q9NVQ8	--MVFSNNDEGLINKKLPKELLRLRIFSFIDVVTLCRCAQISKAWNILALDGSNWQRIDLF	58
20	NOV8	DFQRDIEGRVVENISKRCGGFLRKLSLRGCLGVGDNALRTFAQNCRNIEVLNLNGCTKTI	117
	AAH07557	DFQRDIEGRVVENISKRCGGFLRKLSLRGCLGVGDNALRTFAQNCRNIEVLNLNGCTKTI	117
	Q9CZV8	DFQRDIEGRVVENISKRCGGFLRKLSLRGCLGVGDNALRTFAQNCRNIEVLNLNGCTKTI	117
	Q9UK27	NFQTDVEGRVVENISKRCGGFLRKLSLRGCGIVGDSILKTFQNCRNIEHLNLNGCTKTI	118
	Q9UKA5	NFQIDVEGRVVENISKRCGGFLRKLSLRGCGIVGDSILKTFQNCRNIEHLNLNGCTKTI	120
25	Q9NVQ8	NFQTDVEGRVVENISKRCGGFLRKLSLRGCGIVGDSILKTFQNCRNIEHLNLNGCTKTI	118
30	NOV8	DATCTSLSKFCSKLRHLDLASCTISITNMLKALSEGCPILLEQLNLSWCDQVTKDGIQALV	177
	AAH07557	DATCTSLSKFCSKLRHLDLASCTISITNMLKALSEGCPILLEQLNLSWCDQVTKDGIQALV	177
	Q9CZV8	DATCTSLSKFCSKLRHLDLASCTISITNMLKALSEGCPILLEQLNLSWCDQVTKDGIQALV	177
	Q9UK27	DSTCYLSLRFCSKLRHLDLTSCVSITNSSLKGISEGCRNLEYLNLNSWCDQITKDGIEALV	178
	Q9UKA5	DSTCYLSLRFCSKLRHLDLTSCVSITNSSLKGISEGCRNLEYLNLNSWCDQITKDGIEALV	180
	Q9NVQ8	DSTCYLSLRFCSKLRHLDLTSCVSITNSSLKGISEGCRNLEYLNLNSWCDQITKDGIEALV	178
35	NOV8	RGCGGLKALFLKGCTQLEDEALKYIGAHCPPELVITLNLQTCLOITDEGLITTCRGCHKLOS	237
	AAH07557	RGCGGLKALFLKGCTQLEDEALKYIGAHCPPELVITLNLQTCLOITDEGLITTCRGCHKLOS	237

5	Q9CZV8	RGCGGLKALFLRGCTQLEDEALKVIGAHCPFLVTLNLQTCLOITDEGLTICRGCHKLOS	237
	Q9UK27	RGCRGLKALLLRGCTQLEDEALKHIONYCHELVSLNLQSCSRITDEGVVQICRGCHRLQA	238
	Q9UKA5	RGCRGLKALLLRGCTQLEDEALKHIONYCHELVSLNLQSCSRITDEGVVQICRGCHRLQA	240
	Q9NVQ8	RGCRGLKALLLRGCTQLEDEALKHIONYCHELVSLNLQSCSRITDEGVVQICRGCHRLQA	238
10	NOV8	LCASGCSNITDAIILNALGONCPRLRILEVARCSQLTDVGFTTLARNCHELEKMDLEECVQ	297
	AAH07557	LCASGCSNITDAIILNALGONCPRLRILEVARCSQLTDVGFTTLARNCHELEKMDLEECVQ	297
	Q9CZV8	LCASGCSNITDAIILNALGONCPRLRILEVARCSQLTDVGFTTLARNCHELEKMDLEECVQ	297
	Q9UK27	LCLSGCSNLTDAISLTALGLNCPRLQILEAARCSHLTDAGFTTLARNCHELEKMDLEECIL	298
	Q9UKA5	LCLSGCSNLTDAISLTALGLNCPRLQILEAARCSHLTDAGFTTLARNCHELEKMDLEECIL	300
	Q9NVQ8	LCLSGCSNLTDAISLTALGLNCPRLQILEAARCSHLTDAGFTTLARNCHELEKMDLEECIL	298
15	NOV8	ITDSTLIQLSIHCPRLQVLSLSHCELIITDDGIRHLGNGACAHDQLEVIELDNCPLITDAS	357
	AAH07557	ITDSTLIQLSIHCPRLQVLSLSHCELIITDDGIRHLGNGACAHDQLEVIELDNCPLITDAS	357
	Q9CZV8	ITDSTLIQLSIHCPRLQVLSLSHCELIITDDGIRHLGNGACAHDQLEVIELDNCPLITDAS	357
	Q9UK27	ITDSTLIQLSIHCPKLOALSLSHCELIITDDGILHLSNSTCGHERLRVLELDNCLITDVA	358
	Q9UKA5	ITDSTLIQLSIHCPKLOALSLSHCELIITDDGILHLSNSTCGHERLRVLELDNCLITDVA	360
	Q9NVQ8	ITDSTLIQLSIHCPKLOALSLSHCELIITDDGILHLSNSTCGHERLRVLELDNCLITDVA	358
20	NOV8	LEHLKSCHSLERTELYDCQQITRAGIKRLRTHLEPNIKVHAYFAPVTPPPSVGSSRORFCR	417
	AAH07557	LEHLKSCHSLERTELYDCQQITRAGIKRLRTHLEPNIKVHAYFAPVTPPPSVGSSRORFCR	417
	Q9CZV8	LEHLKSCPSFERIELYDCQQITRAGIKRLRTHLEPNIKVHAYFAPVTPPPSVGSSRORFCR	417
	Q9UK27	LEHLENCRGLERLELYDCQQVTRAGIKRMRAQLPHVKVHAYFAPVTPPTAVAGSGQRLCR	418
	Q9UKA5	LEHLENCRGLERLELYDCQQVTRAGIKRMRAQLPHVKVHAYFAPVTPPTAVAGSGQRLCR	418
25	Q9NVQ8	LEHLENCRGLERLELYDCQQVTRAGIKRMRAQLPHVKVHAYFAPVTPPTAVAGSGQRLCR	418
30	NOV8	CCIIIL	422
	AAH07557	CCIIIL	422
	Q9CZV8	CCIIIL	422
	Q9UK27	CCVII	423
	Q9UKA5	CCVII	425
	Q9NVQ8	CCVII	423

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Domain results for NOV8 were collected from BLAST sample domains found in the Smart and Pfam collections, and then identified by the Interpro domain accession number. The results are listed in Table 8F with the statistics and domain description. These results indicate that the NOV8 polypeptide has properties similar to those of other proteins known to contain these domains and similar to the properties of these domains.

Table 8F. Domain Analysis of NOV8		
PSSMs Producing Significant Alignments	Score (bits)	E Value
F-box: domain 1 of 2, from 9 to 56	29.3	9e-05

F-box	fsllrLPddllekilsrLplkdllslskvskkfrrslvds1.l dv.kl
	+++++ +++++ + +++++ +++++ ++ ++ +++++ ++
NOV8	VINKKLPKELLRLRIFSFLDVVTLCRCAQVSRANVLALDGSNWQrID
	1 (SEQ ID NO:91)
	+
NOV8	L (SEQ ID NO:28)

The Leucine-rich containing F-Box protein-like protein disclosed in this invention is expressed in at least the following tissues: Adrenal Gland, Bladder, Bone marrow, Brain (fetal), Brain (whole), Brain (amygdala), Brain (cerebellum), Brain (hippocampus), Brain (thalamus), Cerebral Cortex, Colorectal, Endothelial cells, Heart, Kidney, Kidney (fetal), Liver, Liver (fetal), Lymph node, Lung, Lung (fetal), Mammary gland, Ovary, Pancreas, Pituitary gland, Placenta, Prostate, Salivary gland, Skeletal Muscle, Small intestine, Spinal cord, Spleen, Stomach, Testis, Trachea, Thymus, Thyroid, Uterus, and several cancer cell lines including Breast ca. (except Breast ca. MDA-N), CNS ca, Colon ca., Gastric ca., Liver ca., Melanoma, Ovarian ca., Pancreatic ca., Prostate ca, and Renal ca. at a measurably higher level than the following tissues: Adipose and one cancer cell line Breast ca. MDA-N. Furthermore, the expression level is even higher in two particular cancer cell lines: Lung ca. (non-s.cl) NCI-H522 and Gastric ca. (liver met) NCI-N87.

The protein similarity information, expression pattern, and map location for the leucine-rich repeats containing F-Box protein-like protein and nucleic acid disclosed herein suggest that this protein may have important structural and/or physiological functions characteristic of the F-Box protein family. Therefore, the NOV8 nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications and as a research tool. For example, since the protein of the invention is ubiquitously expressed in many tissues, the compositions of the present invention will have efficacy for treatment of patients suffering from diseases associated with these tissues. Also since the expression level of the invention is much higher in two particular cancer cell lines: Lung ca. (non-s.cl) NCI-H522 and Gastric ca. (liver met) NCI-N87, the invention may be useful in diagnosis and treatment of these cancers.

The novel nucleic acid encoding the leucine-rich repeats containing F-Box protein-like protein of the invention, or fragments thereof, are useful in diagnostic applications, wherein the

presence or amount of the nucleic acid or the protein are to be assessed. These materials are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. The disclosed NOV8 protein has multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, a contemplated NOV8 epitope is from about amino acids 10 to 15. In another embodiment, a contemplated NOV8 epitope is from about amino acids 40 to 80. In other specific embodiments, contemplated NOV8 epitopes are from about amino acids 85 to 110, 120 to 140, 148 to 150, 155 to 180, 190 to 210, 225 to 230, 240 to 250, 253 to 260, 262 to 270, 275 to 300, 325 to 345, 350 to 400, and 405 to 420.

NOV9

Still yet a further NOVX protein of the invention, referred to herein as NOV9 (alternatively referred to as CG55902-01), is a steroid binding-like protein.

Steroid binding proteins are involved in reproductive behavior, cell cycle progression and various important physiologic pathologies.

The NOV9 protein disclosed herein is predicted to localize extracellularly. Therefore, it is likely that this steroid binding protein-like protein is accessible to a diagnostic probe, and for the various therapeutic applications described herein.

The NOV9 protein disclosed in this invention maps to chromosome 12. This information was assigned using OMIM, the electronic northern bioinformatic tool implemented by CuraGen Corporation, public ESTs, public literature references and/or genomic clone homologies.

The NOV9 nucleic acid (SEQ ID NO:29) of 499 nucleotides encodes a novel steroid binding protein-like protein and is shown in Table 9A. An open reading frame for the mature protein was identified beginning with a ATG initiation codon at nucleotides 19-21 and ending with a TGA codon at nucleotides 442-444. Putative untranslated regions upstream from the start codon and downstream from the termination codon are underlined in Table 9A. The start and stop codons are in bold letters.

Table 9A. NOV9 Nucleotide Sequence (SEQ ID NO:29)

TTCACTGTGGTGGGCCCCATGCCAGGGCAGTGGCTGCAGCAGCTGGCAGTGCCTAGTCCTGATTCTGGTGCTAGCCT
 GGGGGGCTGGTCTACTATGGCAGGAGAAGGATCAGCCCATCTATTTGGCAGTGAAGGGAGTGGGGCTTGATGTCAC
 CTCTGGAAAGGGGTTTATGGACAAAGAGCCCCCTACAATGCCTTGACCAGGAAGGACTCTGCTAGAGGGGTAGCC
 AAGGTGTCCTTGGATCATGTAGACCTTACCTGTGACACAACAGGTCTCATAGCCAAGAAGTTGGAGTCCATGGATG
 ATGTCTTCACCAGTGTGTACAAAGCCAAACACCCAATTGTCAGCTACAGGGCTCAGACAATTCTCAATGAGTTTGG
 CAGCCCCAACCTGGACTTCAAGGCTGAAGACCAGCCCCCTTTTGACAAGAAGGAGGGGTTCTGAGGTTTCATCTGC
 AGGAGCAGGTTTTTGGGAGAGTGAGGTAGGAAGACATTCCAGC

The sequence of NOV9 was derived by laboratory cloning of cDNA fragments covering the full length and/or part of the DNA sequence of the invention, and/or by *in silico* prediction of the full length and/or part of the DNA sequence of the invention from public human sequence databases.

The NOV9 polypeptide (SEQ ID NO:30) encoded by SEQ ID NO:29 is 141 amino acid residues in length and is presented using the one-letter amino acid code in Table 9B. The SignalP, Psort and/or Hydropathy results predict that NOV9 has a signal peptide and is likely to be localized extracellularly with a certainty of 0.8200. In alternative embodiments, a NOV9 polypeptide is located to the microbody (peroxisome) with a certainty of 0.1274, the endoplasmic reticulum (membrane) with a certainty of 0.1000, or the endoplasmic reticulum (lumen) with a certainty of 0.1000.

Table 9B. Encoded NOV9 Protein Sequence (SEQ ID NO:30)

MPGQWLQQLAVLVLIILVLAWGAGLLWQEKDQPIYLAVKGVGLDVTSGKGFYQQRAPYNALTRKDSARGVAKV
 SLDHVDLTCDTTGLIAKKLESMDDVFTSVYKAKHPIVSYRAQTILNEFGSPNLDFKAEDQPLFDKKEGF

The amino acid sequence of NOV9 has high homology to other proteins as shown in Table 9C.

Table 9C. BLASTX Results from Patp Database for NOV9

Sequences Producing High-Scoring Segment Pairs:		High- Score	Smallest Sum Prob P (N)
patp:AAY94866	Human protein clone HP10557	427	2.2e-42
patp:AAB98322	Human PA27 protein	427	4.6e-42
patp:AAY76019	Rat dermal papilla protein DP3	412	6.6e-41
patp:AAB55958	Skin cell protein	412	6.6e-41
patp:AAB98325	Human ortholog of r0v0-176.7A (PA27) protein sequence	240	8.7e-23

In a search of sequence databases, it was found, for example, that the NOV9 nucleic acid sequence of this invention has 392 of 484 bases (80%) identical to a gb:GENBANK-

ID:AF173937|acc:AF173937.1 mRNA from *Homo sapiens* (*Homo sapiens* secreted protein of unknown function (SPUF), mRNA, complete cds). Further, the full amino acid sequence of the disclosed protein of the invention has 85 of 115 amino acid residues (73%) identical to, and 96 of 115 amino acid residues (83%) similar to, the 172 amino acid residue ptmr:SPTREMBL-ACC:Q9UMX5 protein from *Homo sapiens* (Human) (SECRETED PROTEIN OF UNKNOWN FUNCTION).

Additional BLASTP results are shown in Table 9D.

Table 9D. NOV9 BLASTP Results

Gene Index/ Identifier	Protein/Organism	Length of aa	Identity (%)	Positives (%)	Expect Value
Q9UMX5	SECRETED PROTEIN OF UNKNOWN FUNCTION - <i>Homo sapiens</i> (Human)	172	85/115 (73%)	96/115 (83%)	2.8e-42
Q9CQ45	1110060M21RIK PROTEIN - <i>Mus musculus</i> (Mouse)	171	84/115 (73%)	96/115 (83%)	2.3e-39
Q9SK39	PUTATIVE STEROID BINDING PROTEIN - <i>Arabidopsis thaliana</i> (Mouse-ear cress)	100	30/82 (36%)	53/82 (64%)	3.5e-11
Q9FVZ7	PUTATIVE STEROID MEMBRANE BINDING PROTEIN - <i>Oryza sativa</i> (Rice)	232	32/94 (34%)	54/94 (57%)	6.4e-09

A multiple sequence alignment is given in Table 9E in a ClustalW analysis comparing NOV9 with related protein sequences disclosed in Table 9D.

Table 9E. ClustalW Analysis of NOV9

1. SEQ ID NO.: 30	NOV9	4. SEQ ID NO.: 94	Q9SK39
2. SEQ ID NO.: 92	Q9UMX5	5. SEQ ID NO.: 95	Q9FVZ7
3. SEQ ID NO.: 93	Q9CQ45		

NOV9	-----MFGQWLQQLAVLVLLVLA-----WG--	21
Q9UMX5	-----MVGPAERRRRLRPLAALAVLALAP-----GLPTARAGQ	33
Q9CQ45	-----MARPAEWWRIRLLAATVLAALVP-----VPSAWAGQ	32

Q9SK39	-----	1
Q9FVZ7	MAAAVAELWETLKQAI VAYTGLSPAAFFTA VAA AALYH VVSGIFAGPPPPPPPRPRDEP	60
NOV9	-----AGLLWQEKDQPIYLAVKGVGLDVTSGKGFYGRAPYNALTR	62
5 Q9UMX5	TPRPAERGPPVRLFTTEELARYGGEEEDQPIYLAVKGVVFDVTSGKEFYGRGAPYNALTC	93
Q9CQ45	TPRPAERGPPVRLFTTEELARYGGEEEDQPIYLAVKGVVFDVTSGKEFYGRGAPYNALAG	92
Q9SK39	-----MEFTAEQLSOYNGTDESKPIYVAIKGRVFDVTGKSFYSGGDVSMFAG	49
Q9FVZ7	EAEPLPPPVLGEVSEEEELROYDGS DPKPLLMAIKGQIYDVTQSRMFYGPGGPYALFAG	120
10 NOV9	KDSARGVAKVSLDHVDLTCDTTGLIAKKLESMDVFTSVYKAKHPIVSYRAQTILNEFGS	122
Q9UMX5	KDSTRGVAKMSLDEADLTEDTTGLTAKELEALDEVFTKVYKAKYPIVGYTARRILNEDGS	153
Q9CQ45	KDSSRGVAKMSLDEADLTEDTTGLTAKELEALDDVFSKVYKAKYPIVGYTARRILNEDGS	152
Q9SK39	KDASRALGKMSKNEEDVSPSLEGLTEKEINTLND-WETKFEAKYPVVG	96
Q9FVZ7	KDASRALAKMSFEEDLTGDISGLGPFELDALQD-WEYKFMGKYVKVGTVKKTVPVEDGA	179
15 NOV9	PN-----LDFRAEDQPLFDKKEGF-----	141
Q9UMX5	PN-----LDFKPEDQPHFDIKDEF-----	172
Q9CQ45	PN-----LDFKPEDQPHFDIKDEF-----	171
Q9SK39	-----RVVS-----	100
20 Q9FVZ7	PSTSPETTETAAAAEPEKAPATEEKEPREVSSEEVKKEKEDAVAAAAPDEGAKES	232

Domain results for NOV9 were collected from BLAST sample domains found in the Smart and Pfam collections, and then identified by the Interpro domain accession number. The results are listed in Table 9F with the statistics and domain description. These results indicate that the NOV9 polypeptide has properties similar to those of other proteins known to contain these domains and similar to the properties of these domains.

Table 9F. Domain Analysis of NOV9

PSSMs Producing Significant Alignments		Score (bits)	E Value
Steroid Binding Domain (SBD): domain 1 of 1, from 28 to 113		52.2	1.2e-11
SBD	DFTpeELrkYDGsdedkpIylAikGkVYDVtrGrkFYGPgGPYslFA		
	++ +++ ++ ++ ++ + + ++++		
NOV9	-----EK-DQPIYLAVKGVGLDVTSGKGFYGRAPYNALT		
	GrDASRaLatmsfDeedlkdsDeEidDlslLsadeleaLreWetk.FkaK		
	+ + ++++ ++ +++ +++ ++ +++ +++++ ++		
NOV9	RKDSARGVAKVSLDHVDLT-----CDTTGLIAKKLESMDVFTSVYKAK		
	YpvVGrLi (SEQ ID NO:96)		
	++ +		
NOV9	HPIVSYRA (SEQ ID NO:30)		

The steroid binding protein-like protein disclosed in this invention is expressed in a variety of tissues.

The protein similarity information, expression pattern, and map location for the steroid binding protein-like protein and nucleic acid disclosed herein suggest that this protein may have important structural and/or physiological functions characteristic of the steroid binding protein family. Therefore, the NOV9 nucleic acids and proteins of the invention are useful in potential
5 diagnostic and therapeutic applications and as a research tool. For example, the compositions of the present invention will have efficacy for treatment of patients suffering from: cancer, cataracts, obesity, diabetes, hyperlipidemia, infertility, inflammation, CNS disorders and other diseases, disorders and conditions of the like.

The novel nucleic acid encoding the steroid binding protein-like protein of the invention,
10 or fragments thereof, are useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed. These materials are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX
15 Antibodies" section below. The disclosed NOV9 protein has multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, a contemplated NOV9 epitope is from about amino acids 25 to 37. In another embodiment, a contemplated NOV9 epitope is from about amino acids 42 to 78. In other specific embodiments, contemplated NOV9 epitopes are from about amino acids 81 to 92, and 95 to 135.

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NOV10

Another NOVX protein of the invention, referred to herein as NOV10, includes two novel steroid dehydrogenase-like proteins. The disclosed proteins have been named NOV10a and NOV10b.

25

Steroid dehydrogenase enzymes influence mammalian reproduction, hypertension, neoplasia, and digestion. The three-dimensional structures of steroid dehydrogenase enzymes reveal the position of the catalytic triad, a possible mechanism of keto-hydroxyl interconversion, a molecular mechanism of inhibition, and the basis for selectivity.

The NOV10 proteins disclosed here are predicted to localize at the plasma membrane.
30 Therefore, it is likely that these proteins are accessible to a diagnostic probe, and for the various therapeutic applications described herein.

The NOV10 proteins in this invention map to chromosome 16. This information was assigned using OMIM, the electronic northern bioinformatic tool implemented by CuraGen Corporation, public ESTs, public literature references and/or genomic clone homologies.

NOV10a

In one embodiment, a NOV10 variant is NOV10a (alternatively referred to herein as CG50307-01), which encodes a novel steroid dehydrogenase-like protein and includes the 1831 nucleotide sequence (SEQ ID NO:31) shown in Table 10A. An open reading frame for the mature protein was identified beginning with an ATG codon at nucleotides 183-185 and ending with a TGA codon at nucleotides 1173-1175. Putative untranslated regions downstream from the termination codon and upstream from the initiation codon are underlined in Table 10A, and the start and stop codons are in bold letters.

Table 10A. NOV10a Nucleotide Sequence (SEQ ID NO:31)

ACCGGTTTGGAAAGACTTTGCCGGCCTGCAGGACACATGATGACATTGGACCCACCCTCCCCAGCTCGGAGTCTT
TAACTCAGTCACATCTACGGAGTCCCTTTGGCCACATAAGATTGGCCTTAAGAGAAGGACGGAGCCACATACTG
CTGACGGCCAGAACTGGCAGAGAGAAGGTTGCCATGGCTGCTGTTGACAGTTTCTACCTCTTGTACAGGGAAA
TCGCCAGGTCTTGCAATTGCTATATGGAAGCTCTAGCTTTGGTTGGAGCCTGGTATACGGCCAGAAAAAGCATC
ACTGTCACTCTGTGACTTTTACAGCCTGATCAGGCTGCATTTTATCCCCCGCCTGGGGAGCAGAGCAGACTTGAT
CAAGCAGTATGGAAGATGGGCCGTTGTGTCAGCGGTGCAACAGATGGGATTGGAAAAGCCTACGCTGAAGAGTTAG
CAAGCCGAGGTCTCAATATAATCCTGATTAGTCGGAACGAGGAGAAGTTGCAGGTTGTTGCTAAAGACATAGCC
GACACGTACAAAGTGGAAGCTGATATTATAGTTGCGGACTTCAGCAGCGGTGTCGAGATCTACCTTCCAATTG
AGAAGCCCTGAAGGACAAAGACGTTGGCATCTTGGTAAATAACGTGGGTGTGTTTTATCCCTACCCGCAGTATT
TCACTCAGCTGTCCGAGGACAAGCTCTGGGACATCATAAATGTGAACATTGCCGCCGCTAGTTTGTATGGTCCAT
GTTGTGTTACCGGGAATGGTGGAGAGAAAGAAAGGTGCCATCGTCACGATCTCTTCTGGCTCCTGCTGCAAAACC
CACTCCTCAGCTGGCTGCATTTTCTGCTTCTAAGGCTTATTTAGACCACCTTCAGCAGAGCCTTGCAATATGAAT
ATGCCTCTAAAGGAATCTTTGTACAGAGTCTAATCCCTTTCTATGTAGCCACCAGCATGACAGCACCAGCAAC
TTTCTGCACAGGTGCTCGTGGTTGGTGCCTTCGCCAAAAGTCTATGCACATCATGCTGTTTCTACTCTTGGGAT
TTCCAAAAGGACCACAGGATATTGGTCCATTCTATTAGTTTCTTTTGCACAGTATATGCCTGAATGGCTCT
GGGTGTGGGGAGCAAATATTCTCAACCGTTCACTACGTAAGGAAGCCTTATCCTGCACAGCCTGAGTCTGGATG
GCCACTTGAGAAGTTTGGCCAACTCCTGGGAACCTCGATATTCTGACATTTGGAAAAACACATTTAATTTATCT
CCTGTGTTTCATTGCTGATTATTACAGCATACTGTTGATTGCTCATTTGCAAAACACACATAATACCGTCAGAGT
GCTGTGAAAAACCTTAAGGGTGTGTGGATGGCACAGGATCAATAATGCCTGAGGCTGATTGACGACATCTACAT
TTCACTGCTTTTCCCTAAGCTGTTTGAAAGTTACGCTTTTCTGTTGTTCTAGAGCCACAGCAGTCTAATATTG
AAATATAATATGATTGTCAGGTCTTATAATTTAGATGTTGTTTTTAAAGGGAATTGACCATTTCACTAGAGG
AGTTGTGCTGGTTTTTACATGTGCATCAAGGAAAGACTACTGGAAAAGTATTTATTTTGGTAACTAAGATTGCT
GGCTACTATTAGGGACACACTCCGGGCTGTTTGGTATAGCTCTACCTGGTTTGACTATCTGTCTATGGAAATGCT
GCCTTCCACTGGTTTTTCCCTTGAGACGGGGTGTGTGCCTGGGTTGTGGGGCCCTTGGGCCCTTTTTTTTGGT
GCCCTTCTTCCACCCACTTTCCGGCCCGGGCCCCCTGGCGCTCTGGGTTTCCC

The sequence of NOV10a was derived by laboratory cloning of cDNA fragments, by *in silico* prediction of the sequence. The cDNA fragments covering either the full length of the DNA

sequence, or part of the sequence, or both, were cloned. *In silico* prediction was based on sequences available in CuraGen's proprietary sequence databases or in the public human sequence databases, and provided either the full length DNA sequence, or some portion thereof.

The DNA sequence and protein sequence for a novel transmembrane-like gene were obtained by SeqCalling™ Technology and are reported here as NOV10a. These methods used to amplify NOV10a cDNA are described in Example 2.

The NOV10a polypeptide (SEQ ID NO:32) encoded by SEQ ID NO:31 is 330 amino acid residues in length and is presented using the one-letter amino acid code in Table 10B. The SignalP, Psort and/or Hydropathy results predict that NOV10a has no known signal peptide and is likely to be localized at the plasma membrane with a certainty of 0.7000. In alternative embodiments, a NOV10a polypeptide is located to the mitochondrial inner membrane with a certainty of 0.6577, the microbody (peroxisome) with a certainty of 0.4556, or the mitochondrial matrix space with a certainty of 0.2792.

Table 10B. Encoded NOV10a Protein Sequence (SEQ ID NO:32)

MAAVDSFYLLYREIARSCNCYMEALALVGAWYTARKSITVICDFYSLIRLHFIPRLGSRADLIKQYGRWAVVSGA TDGIGKAYAEELASRGLNIILISRNEEKLVVAKDIADTYKVETDIIVADFSSGREIYLPIREALKDKDVGILVN NVGVFYPPYQYFTQLSEDKLWDIINVNIAAASLMVHVLPGMVERKKGAIVTISGSCCKPTPQLAAFSASKAYL DHFSRALQYFYASKGIFVQSLIPFYVATSMTAPSNFLHRCSWLVPSPKVYAHHAVSTLGISKRTTGYWSHSIQFL FAQYMPPEWLWVWGANILNRSRLRKEALSCTA

NOV10b

In an alternative embodiment, a NOV10 variant is NOV10b (alternatively referred to herein as CG50307-02), which includes the 1152 nucleotide sequence (SEQ ID NO:33) shown in Table 10C. An open reading frame for the mature protein was identified beginning with an ATG codon at nucleotides 97-99 and ending with a TGA codon at nucleotides 1087-1089. The start and stop codons of the open reading frame are highlighted in bold type. Putative untranslated regions are underlined and found upstream from the initiation codon and downstream from the termination codon.

Table 10C. NOV10b Nucleotide Sequence (SEQ ID NO:33)

ATCTACGGAGTCCCTTTGGCCACATAAGATTGGCCTTAAGAGAAGGACGGAGCCACATACTGCTGACGGCCCAGAA
 CTGGCAGAGAGAAGGTTGCCATGGCTGCTGTTGACAGTTTCTACCTCTTGTACAGGGAAATCGCCAGGTCTTGCAA
 TTGCTATATGGAAGCTCTAGCTTTGGTTGGAGCCTGGTATACGGCCAGAAAAAGCATCACTGTCATCTGTGACTTT
 TACAGCCTGATCAGGCTGCATTTTATCCCCGCCTGGGGAGCAGAGCAGACTTGATCAAGCAGTATGGAAGATGGG
 CCGTTGTCAGCGGTGCAACAGATGGGATTGGAAGCCTACGCTGAAGAGTTAGCAAGCCGAGGTCTCAATATAAT
 CCTGATTAGTCGGAACGAGGAGAAGTTGCAGGTTGTTGCTAAAGACATAGCCGACACGTACAAAGTGGAACTGAT
 ATTATAGTTGCGGACTTCAGCAGCGGTCGTGAGATCTACCTTCCAATTCGAGAAGCCCTGAAGGACAAAGACGTTG
 GCATCTTGGTAAATAACGTGGGTGTGTTTTATCCCTACCCGCACTATTTCACTCAGCTGTCCGAGGACAAGCTCTG
 GGACATCATAAATGTGAACATTGCCGCCGCTAGTTTGTATGGTCCATGTTGTGTTACCGGGAATGGTGGAGAGAAAG
 AAAGGTGCCATCGTCACGATCTCTTCTGGCTCCTGCTGCAAACCCACTCCTCAGCTGGCTGCATTTTCTGCTTCTA
 AGGCTTATTTAGACCCTTCAGCAGAGCCTTGCAATATGAATATGCCTCTAAAGGAATCTTTGTACAGAGTCTAAT
 CCCTTTCTATGTAGCCACCAGCATGACAGCACCAGCAACTTTCTGCACAGGTGCTCGTGGTTGGTGCCTTCGCCA
 AAAGTCTATGCACATCATGCTGTTTCTACTCTTGGGATTTCCAAAAGGACCACAGGATATTGGTCCCATTCTATTC
 AGTTTCTTTTGCACAGTATATGCCTGAATGGCTCTGGGTGTGGGGAGCAAATATTCTCAACCGTTCACTACGTAA
 GGAAGCCTTATGCTGCACAGCCTGAGTCTGGATGGCCACTTGAGAAGTTTGGCAACTCCTGGGAACCTCGATATT
 CTGACATTTGGA

The sequence of NOV10b was derived by laboratory cloning of cDNA fragments, by *in silico* prediction of the sequence. The cDNA fragments covering either the full length of the DNA sequence, or part of the sequence, or both, were cloned. *In silico* prediction was based on sequences available in CuraGen's proprietary sequence databases or in the public human sequence databases, and provided either the full length DNA sequence, or some portion thereof.

The cDNA coding for the NOV10b sequence was cloned by the polymerase chain reaction (PCR). Primers were designed based on *in silico* predictions of the full length or some portion (one or more exons) of the cDNA/protein sequence of the invention, or by translated homology of the predicted exons to closely related human sequences or to sequences from other species. The DNA sequence and protein sequence for a novel transmembrane-like gene were obtained by exon linking and are reported here as NOV10b. These primers and methods used to amplify NOV10b cDNA are described in Example 2.

The NOV10b polypeptide (SEQ ID NO:34) encoded by SEQ ID NO:33 is 330 amino acid residues in length and is presented using the one-letter amino acid code in Table 10D. The SignalP, Psort and/or Hydropathy results predict that NOV10b has no known signal peptide and is likely to be localized at the plasma membrane with a certainty of 0.7000. In alternative embodiments, a NOV10b polypeptide is located to the mitochondrial inner membrane with a certainty of 0.6577, the microbody (peroxisome) with a certainty of 0.4320, or the mitochondrial matrix space with a certainty of 0.2792..

Table 10D. Encoded NOV10b Protein Sequence (SEQ ID NO:34)

MAAVDSFYLLYREIARSCNCYMEALALVGAWYTARKSITVICDFYSLIRLHFIPRLGSRADLIKQYGRWAVVSGA
 TDGIGKAYAEELASRGLNIILISRNEEKLVVAKDIADTYKVETDIIVADFSSGREIYLPIREALKDKDVGILVN
 NVGVFYYPYPQYFTQLSEDKLWDIINVNIAAASLMVHVLPGMVERKKGAIVTISSGSCCKPTPOLAAFSASKAYL
 DHFSRALQYFYASKGIFVQSLIPFYVATSMTAPSNFLHRCWLVPSPKVYAHHAVSTLGISKRTTGYWSHSIQFL
 FAQYMPPEWLWVWGAILNRSRLRKEALCCTA

SNP variants of NOV10 are disclosed in Example 3.

NOV10 Clones

5 Unless specifically addressed as NOV10a or NOV10b, any reference to NOV10 is assumed to encompass all variants.

The amino acid sequence of NOV10 has high homolgy to other proteins as shown in Table 10E.

Table 10E. BLASTX Results from Patp Database for NOV10

Sequences Producing High-Scoring Segment Pairs:		High Score	Smallest Sum Prob P (N)
patp:AAM39603	Human polypeptide	1715	2.2e-176
patp:AAM41389	Human polypeptide	1715	2.2e-176
patp:AAM93392	Human polypeptide	1710	7.4e-176
patp:AAU18335	Human endocrine polypeptide	1449	3.4e-148
patp:AAM42370	Human polypeptide	1264	1.4e-128

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In a search of sequence databases, it was found, for example, that the NOV10a nucleic acid sequence of this invention has 859 of 899 bases (95%) identical to a gb:GENBANK-ID:AK025626|acc:AK025626.1 mRNA from Homo sapiens (Homo sapiens cDNA: FLJ21973 fis, clone HEP05846). Further, the full amino acid sequence of the disclosed NOV10a protein of the invention has 123 of 302 amino acid residues (40%) identical to, and 188 of 302 amino acid residues (62%) similar to, the 312 amino acid residue ptrn:SPTREMBL-ACC:Q9Y6G8 protein from Homo sapiens (Human) (STEROID DEHYDROGENASE HOMOLOG).

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In a similar search of sequence databases, it was found, for example, that the NOV10b nucleic acid sequence of this invention has 350 of 351 bases (99%) identical to a gb:GENBANK-ID:AK025626|acc:AK025626.1 mRNA from Homo sapiens (Homo sapiens cDNA: FLJ21973 fis, clone HEP05846). Further, the full amino acid sequence of the disclosed protein of the invention

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has 122 of 299 amino acid residues (40%) identical to, and 187 of 299 amino acid residues (62%) similar to, the 312 amino acid residue ptrn:SPTREMBL-ACC:Q9Y6G8 protein from Homo sapiens (Human) (STEROID DEHYDROGENASE HOMOLOG).

Additional BLASTP results are shown in Table 10F.

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Table 10F. NOV10 BLASTP Results

Gene Index/ Identifier	Protein/Organism	Length of aa	Identity (%)	Positives (%)	Expect Value
Q9BY22	STEROID DEHYDROGENASE-LIKE PROTEIN - Homo sapiens (Human)	309	309/309 (100%)	309/309 (100%)	2.6e-164
Q9VJG9	CG13284 PROTEIN - Drosophila melanogaster (Fruit fly)	339	125/310 (40%)	191/310 (61%)	9.5e-57
Q9Y6G8	STEROID DEHYDROGENASE HOMOLOG - Homo sapiens (Human)	312	123/302 (40%)	188/302 (62%)	2.5e-56
O57314	Putative steroid dehydrogenase SPM2 (EC 1.1.1.-) - Anas platyrhynchos (Domestic duck)	312	121/228 (50%)	163/238 (68%)	5.3e-56
O70503	Putative steroid dehydrogenase KIK-I (EC 1.1.1.-) - Mus musculus (Mouse)	312	122/281 (43%)	180/281 (64%)	3.7e-55

A multiple sequence alignment is given in Table 10G, with the NOV10 protein of the invention being shown in lines 1 and 2, in a ClustalW analysis comparing NOV10 with related protein sequences of Table 10F.

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Table 10G. ClustalW Analysis of NOV10

15	1. SEQ ID NO.: 32	NOV10a	5. SEQ ID NO.: 99	Q9Y6G8
	2. SEQ ID NO.: 34	NOV10b	6. SEQ ID NO.: 100	O57314
	3. SEQ ID NO.: 97	Q9BY22	7. SEQ ID NO.: 101	O70503
	4. SEQ ID NO.: 98	Q9VJG9		
20	NOV10a	-MAAVDSFYLLYREIARSCNCYMEALALVGAWYTARKSLITVICDFYSLIRLHFDPRLG--	57	
	NOV10b	-MAAVDSFYLLYREIARSCNCYMEALALVGAWYTARKSLITVICDFYSLIRLHFDPRLG--	57	
	Q9BY22	-----MEALALVGAWYTARKSLITVICDFYSLIRLHFDPRLG--	36	

	Q9VJG9	MQPVLEVSIIYTLKMAFIWQLISAATYLVGLLTIGVFLYDNLKSLVSIITKAVLEPYFQPH	60
	Q9Y6G8	-----MESALPAAGFLYWVGAGTVAYLAIRISYSLFTALRVWGVGN----	41
	O57314	-----MLPAAGLLWWVCALGALYA AVRGA LGLLGA LRWVGIGAG----	39
5	O70503	-----MECAPPAAGFLYWVGASTIAYLALRASYSLFRAFQVWCVGN----	41
	NOV10a	SRADLIKQYGRWAVVSGATDGIGKAYAEELASRGLNIILISRNEEKLOVVAKDIADTYKV	117
	NOV10b	SRADLIKQYGRWAVVSGATDGIGKAYAEELASRGLNIILISRNEEKLOVVAKDIADTYKV	117
	Q9BY22	SRADLIKQYGRWAVVSGATDGIGKAYAEELASRGLNIILISRNEEKLOVVAKDIADTYKV	96
10	Q9VJG9	LPRTLIVDKFGQWAVVTGATDGIGKEYARELARQGINLVILISRTKEKLI AVTNEIESQYKV	120
	Q9Y6G8	-EAGVGPGLGEWAVVTGSTDGIGKSYAEELAKHGMKVVLISRSKDKLDQVSSEIKEKFKV	100
	O57314	-RAALGPGLCAWAVVTGATDGIGKAYAKELAKRMKVVALISRSKEKLDQVAGEITEQYGV	98
	O70503	-EALVGPRLGEWAVVTGGTDGIGKAYAEELAKRMKIVLISRSQDKLNOVSNNIKEKENV	100
	NOV10a	ETDIIVADFSSGREIYLP IREALKDKDV GILVNNVGVFYPYPQYFTQLS--EDKLWDIIN	175
15	NOV10b	ETDIIVADFSSGREIYLP IREALKDKDV GILVNNVGVFYPYPQYFTQLS--EDKLWDIIN	175
	Q9BY22	ETDIIVADFSSGREIYLP IREALKDKDV GILVNNVGVFYPYPQYFTQLS--EDKLWDIIN	154
	Q9VJG9	RTKWIAADFAKGREVYDQTEKELAGIDVGILVNNVGMVYEHPESLDLVS--EDLLWNLLT	178
	Q9Y6G8	ETRTIIVADFA-SEDIYDKIKTGLAGLEIGILVNNVGMVSEYEPYFLDVPDLDNVKKMIN	159
20	O57314	ETKVIIVADFERED IYDRIRAGLEGLEIGVLVNNVGISYSYPEYFIDVPDLDKTIDKMIN	158
	O70503	ETRTIIVADFSS-LDDIYDKIKTGLSGLLEIGVLVNNVGMVSEYEPYFLETPDLDNITKKMIN	159
	NOV10a	VNIAAASLMVHVLPGMVERKKGAIVTISSGSCCKPTPOLAAFSASKAYLDHFSRALQYE	235
	NOV10b	VNIAAASLMVHVLPGMVERKKGAIVTISSGSCCKPTPOLAAFSASKAYLDHFSRALQYE	235
25	Q9BY22	VNIAAASLMVHVLPGMVERKKGAIVTISSGSCCKPTPOLAAFSASKAYLDHFSRALQYE	214
	Q9VJG9	VVMGSVTMLTRKILPQMIGRRKGAVNLGSSSELOPLNMTVYAASKFVTYFSKALELE	238
	Q9Y6G8	INILSVCKMTQVLVLPGMVERSKGAILNIISSGSMLEVPPLLTITYSATKTFVDFFSQCLHEE	219
	O57314	INIMSVCKMTRIVLPGMVERSKGVILNIISSAAGMYPTPLLTITLYSASKAFVDYFSRGLHAE	218
	O70503	INVLSVCKVTRIVLPGMVERSKGVILNIISSASGMLPVELLTITYSATKAFVDFFSQCLHEE	219
30	NOV10a	YASKGIFVQSLIPFYVATSMTAPSNFLHRCSWLVPSPKVYAHHAVSTLGISKRTTGYWSH	295
	NOV10b	YASKGIFVQSLIPFYVATSMTAPSNFLHRCSWLVPSPKVYAHHAVSTLGISKRTTGYWSH	295
	Q9BY22	YASKGIFVQSLIPFYVATSMTAPSNFLHRCSWLVPSPKVYAHHAVSTLGISKRTTGYWSH	274
	Q9VJG9	VAEHNTHVQLVMPNFFVTKMAYTDRVMQGLFFENAYTFARS AVFTLGKTSETNGEWFTH	298
35	Q9Y6G8	YRSKGMFVQSVLPYFVATKIAK-----IRKPTLDKPSPETFVKSAIKTVGLQSRITNGYLIH	275
	O57314	YKSKGILVQSVMPYFVATKMSK-----ISKPSFDKPTPETYVRAAIGTVGLQSQITNGCLPH	274
	O70503	YKSKGIFVQSVMPYFVATKIAK-----IQKPTLDKPSAETFVKSAIKTVGLQTRITNGYVIE	275
	NOV10a	SIQFLFAQYMPPEWLWVWGANILNRSRLKEALSCTA-----	330
	NOV10b	SIQFLFAQYMPPEWLWVWGANILNRSRLKEALSCTA-----	330
40	Q9BY22	SIQFLFAQYMPPEWLWVWGANILNRSRLKEALSCTA-----	309
	Q9VJG9	GIOYAIMKLAPLPRTYLGHQIFKRLRIEALQKQKKLKL	339
	Q9Y6G8	ALMGSIISNLPSWIYLIKIVMNMNKSTRAHYLKKTCKN----	312
	O57314	AFMGWVFSILPTSTVMNLLMKTINKQIRARFLKKMKKEK---	312
45	O70503	SLMGSIINSIMPRWYFKIIMGFSKSLRNRYLKKRCKN----	312

Domain results for NOV10 were collected from the Pfam database, and then identified by the Interpro domain accession number. The results are listed in Table 10H with the statistics and domain description. These results indicate that the NOV10 polypeptides have properties similar to those of other proteins known to contain these domains.

Table 10H. Domain Analysis of NOV10

PSSMs Producing Significant Alignments		Score (bits)	E Value
Short Chain Alcohol Dehydrogenase (adh_short): domain 1 of 1, from 66 to 306		95.6	9.8e-25
ADH Short	tgKvaLvTGassGIGlaiAkrLakeGakVvvvdrreekaeqvaaelk ++++++ ++ +++ ++ +++ +++++ ++++++ +++ ++		
NOV10a	YGRWAVVSGATDGIGKAYAEELASRGLNIILISRNEEKLOVVAKDIA aelGdralfiqlDvtdeeqvkaavaqaverlGd.rlDvLVNNAGilgpgp + ++ +++ ++ + + +++++ ++ + + + + + +		
NOV10a	DTYKVVETDIIVADFSSGRE---IYLPiREALKDKDVGILVNNVGVFYPYP pfe.elseedwervidvNltGvflItqavlpamdhlkrkgGrIvNisSv + +++++ +++++ + ++ +++ +++ + +++++ + ++		
NOV10a	QYFtQLSEDKLWDIINVNIAAASLMVHVLP---GMVERKKGAIVTISSG aGlnvgvpglSaYsASKaavigltrsLAlElaphgtgIrVnavaPGgvdT ++ ++ +++++ + + + +++++ + ++ ++ + +++		
NOV10a	SCC-KPTPQLAAFSASKAYLDHFSRALQYEYASKG--IFVQSLIPFYVAT dmtkalrsrlieakkkvrevadiadpeleerits.titplgrygv.tpee ++++ ++ + + + + + + + + + + + + + + + + + + +		
NOV10a	SMTAPSN-----FLHRCswLV-PSPKVYAhHAVs ianavlfLasdgasysvtggtlnvdggl (SEQ ID NO:102) ++ + ++ + +++++ +		
NOV10a	TLGISKRRTGYWSHS---IQFLFAQYMP (SEQ ID NO:32)		

The NOV10 proteins disclosed in this invention is expressed in at least the following tissues: adrenal gland/suprarenal gland, bone, bone marrow, brain – whole, brain – hippocampus, brain - hypothalamus, dermis, epidermis, hair follicles, lymph node, t-cell, eye, ovary and testis. This information was derived by determining the tissue sources of the sequences that were included in the invention including but not limited to SeqCalling sources, Public EST sources, Literature sources, and/or RACE sources.

The protein similarity information, expression pattern, and map location for the steroid dehydrogenase-like protein and nucleic acid disclosed herein suggest that this protein may have important structural and/or physiological functions characteristic of the steroid dehydrogenase family. Therefore, the nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications and as a research tool. For example, the compositions of the present invention will have efficacy for treatment of patients suffering from: cardiomyopathy, atherosclerosis, hypertension, congenital heart defects, aortic stenosis, atrial septal defect (ASD),

atrioventricular (A-V) canal defect, ductus arteriosus, pulmonary stenosis, subaortic stenosis, ventricular septal defect (VSD), valve diseases, tuberous sclerosis, scleroderma, obesity, adrenoleukodystrophy, congenital adrenal hyperplasia, neoplasia, diabetes, digestion, Von Hippel-Lindau (VHL) syndrome, cirrhosis, pancreatitis, endometriosis, fertility, hemophilia, hypercoagulation, idiopathic thrombocytopenic purpura, autoimmune disease, allergies, immunodeficiencies, transplantation, graft versus host disease, osteoporosis, hypercalcaemia, arthritis, ankylosing spondylitis, scoliosis, muscular dystrophy, Lesch-Nyhan syndrome, myasthenia gravis, Alzheimer's disease, stroke, tuberous sclerosis, hypercalcaemia, Parkinson's disease, Huntington's disease, cerebral palsy, epilepsy, Lesch-Nyhan syndrome, multiple sclerosis, ataxia-telangiectasia, leukodystrophies, behavioral disorders, addiction, anxiety, pain, neuroprotection, psoriasis, actinic keratosis, acne, hair growth/loss, alopecia, pigmentation disorders, endocrine disorders, and other diseases, disorders and conditions of the like.

The novel nucleic acid encoding the steroid dehydrogenase-like protein of the invention, or fragments thereof, are useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed. These materials are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. The disclosed NOV10 protein has multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, a contemplated NOV10 epitope is from about amino acids 10 to 15. In another embodiment, a contemplated NOV10 epitope is from about amino acids 50 to 70. In other specific embodiments, contemplated NOV10 epitopes are from about amino acids 75 to 80, 80 to 85, 85 to 95, 100 to 110, 120 to 125, 125 to 140, 155 to 175, 200 to 205, 210 to 215, 215 to 225, 225 to 240, 260 to 275, 275 to 300, and 310 to 325.

NOV11

Yet a further NOVX protein of the invention, referred to herein as NOV11 (alternatively referred to as CG50311-01), is a myosin heavy chain-like protein.

Myosins are molecular motors that upon interaction with actin filaments convert energy from ATP hydrolysis into mechanical force. Myosins can be divided into at least three main classes, with two types of unconventional myosin being no more related to each other than they

are to conventional myosin. Myosins have traditionally been classified as conventional or unconventional, with many of the unconventional myosin proteins thought to be distributed in a narrow range of organisms. Members of all three of these main classes are likely to be present in most or all eukaryotes.

5 Although SignalP, Psort and/or hydropathy suggest that the myosin heavy chain-like protein may be localized in the nucleus, the NOV11 protein predicted here is similar to the myosin heavy chain family, some members of which are expected to have intracellular sub-cellular localization. Therefore it is likely that this novel myosin heavy chain-like protein is available at the same sub-cellular localization and hence accessible to a diagnostic probe and for
10 various therapeutic applications.

The NOV11 protein disclosed in this invention maps to chromosome 22. This information was assigned using OMIM, the electronic northern bioinformatic tool implemented by CuraGen Corporation, public ESTs, public literature references and/or genomic clone homologies.

15 The NOV11 nucleic acid (SEQ ID NO:35) of 7396 nucleotides encodes a novel myosin heavy chain-like protein and is shown in Table 11A. An open reading frame for the mature protein was identified beginning with a ATG initiation codon at nucleotides 140-142 and ending with a TAA codon at nucleotides 6017-6019. Putative untranslated regions upstream from the start codon and downstream from the termination codon are underlined in Table 11A. The start and stop codons are in bold letters.

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Table 11A. NOV11 Nucleotide Sequence (SEQ ID NO:35)

<p> <u>CAAGGCTGACCTGCTGCAGCTCCCGCCTCGTGCGCTCGCCCCACCCGGCCGCGCCCGAGCGCTCGAGAAAGTC</u> <u>CTCTCGGGAGAAGCAGCGCCTGTTCCCGGGGCAGATCCAGGTTTCAGGTCCTGGCTATAAGTCACCATGGCACAG</u> <u>CAAGCTGCCGATAAGTATCTCTATGTGGATAAAAACTTCATCAACAATCCGCTGGCCCAGGCCGACTGGGCTGC</u> <u>CAAGAAGCTGGTATGGGTGCCTTCCGACAAGAGTGGCTTTGAGCCAGCCAGCCTCAAGGAGGAGGTGGGCGAAG</u> <u>AGGCCATCGTGGAGCTGGTGGAGAATGGGAAGAAGGTGAAGGTGAACAAGGATGACATCCAGAAGATGAACCCG</u> <u>CCCAAGTTCTCCAAGGTGGAGGACATGGCAGAGCTCACGTGCCTCAACGAAGCCTCGGTGCTGCACAACCTCAA</u> <u>GGAGCGTTACTACTCAGGGCTCATCTACACCTATTACAGGCCTGTTCTGTGTGGTTCATCAATCCTTACAAGAACC</u> <u>TGCCCATCTACTCTGAAGAGATTGTGGAAATGTACAAGGGCAAGAAGAGGCACGAGATGCCCCCTCACATCTAT</u> <u>GCCATCACAGACACCGCTACAGGAGTATGATGCAAGACCGAGAAGATCAATCCATCTTGTGCACTGGTGAATC</u> <u>TGGAGCTGGCAAGACGGGAGAACACCAAGAAGGTTCATCCAGTATCTGGCGTACGTGGCGTCCCTCGCACAAAGAGCA</u> <u>AGAAGGACCAGGGCGAGCTGGAGCGGCAGCTGCTGCAGGCCAACCCCATCCTGGAGGCCTTCGGGAACGCCAAG</u> <u>ACCGTGAAGAATGACAACTCCTCCGCTTCGGCAAATTCATTGCGATCAACTTTGATGTCAATGGCTACATTGT</u> <u>TGGAGCCAACTGAGACTTATCTTTTGGAGAAATCTCGTGCTATCCGCCAAGCCAAGGAAGAACGGACCTTCC</u> <u>ACATCTTCTATTATCTCCTGTCTGGGGCTGGAGAGCACCTGAAGACCGATCTCCTGTTGGAGCCGTACAACAAA</u> <u>TACCGCTTCTGTTCATTCAGTACCGTACCATCCCCGGGCAGGACAGGACATGTTCCAGGAGACCATGGA</u> <u>GGCCATGAGGATTATGGGCATCCAGAAGAGGAGCAAATGGGCCTGCTGCGGGTCATCTCAGGGGTTCTTCAGC</u> <u>TCGGCAACATCGTCTTCAAGAAGGAGCGGAACACTGACAGGCGTCCATGCCCCGACAACACAGCTGCCCAAAAG</u> </p>
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GTGTCCCATCTCTTGGGTATCAATGTGACCGATTTACCAGAGGAATCCTCACCCCGCGCATCAAGGTGGGACG
GGATTACGTCCAGAAGGCGCAGACTAAAGAGCAGGCTGACTTTGCCATCGAGGCCCTTGCCCAAGGCGACCTATG
AGCGGATGTTCCGCTGGCTGGTGCTGCGCATCAACAAGGCTCTGGACAAGACCAAGAGGCGAGGCGCCTCTTC
ATCGGGATCCTGGACATTGCCGGCTTCGAGATCTTTGATCTGAACCTCGTTTGAGCAGCTGTGCATCAATTACAC
CAATGAGAAGCTGCAGCAGCTCTTCAACCACACCATGTTTCATCCTGGAGCAGGAGGAGTACCAGCGCGAGGGCA
TCGAGTGGAACTTCATCGACTTTGGCCTCGACCTGCAGCCCTGCATCGACCTCATTGAGAAGCCAGCAGGCCCC
CCGGGCACTTCTGGCCCTGCTGGACGAGGAGTGCTGGTTCCCAAGGCCACCGACAAGAGCTTCGTGGAGAAGGT
GATGCAGGAGCAGGGCACCCACCCCAAGTTCCAGAAGCCCAAGCAGCTGAAGGACAAAGCTGATTTCTGCATTA
TCCACTATGCCCGCAAGGTGGATTACAAAGCTGACGAGTGGCTGATGAAGAACATGGATCCCTGAAATGACAAC
ATCGCCACACTGCTCCACAGTCTCTGACAAGTTGTCTCGGAGCTGTGGAAGGATGTGGACCGCATCATCGG
CCTGGACCAGGTGGCCGGCATGTGCGAGACCGCACTGCCCGGGCCTTCAAGACGCGGAAGGGCATGTTCCGCA
CTGTGGGGCAGCTTTACAAGGAGCAGCTGGCCCAAGCTGATGGCTACGCTGAGGAACACGAACCCCAACTTTGTC
CGCTGCATCATCCCCAACACGAGAAGAAGGCCCGGCAAGCTGGAGACCCGCATCTCGTGCTGGACCAGCTGCGCTG
CAACGGTGTCTCGAGGGCATCCGTATCTGCCGCCAGGGCTTCCCAACAGGGTGGTCTTCCAGGAGTTTCGGC
AGAGATATGAGATCCTGACTCCAACTCCATTCCCAAGGGTTTTCAGCTGAAGGACAAAGCTGATTTCTGCATTA
ATAAAGCCCTGGAGCTCGACAGCAATCTGTACCGATTGGCCAGAGCAAAGTCTTCTCCGTGCCGGTGTGCT
GGCCACCTGGAGGAGGAGCGAGACCTGAAGATCACCGACGTATCATAGGGTTCCAGGCTGTGTCAGGGGCT
ACCTGGCCAGGAAAGCATTTGCCAAGCGGCAGCAGCAGCTTACCGCCATGAAGGTCTTCCAGCGAACTGCGCT
GCCTACCTGAAGCTGCGGAAGTGGCAGTGGTGGCGGCTCTTACCAAGGTCAAGCCGCTGCTGCGAGGAGCGG
GCAGGAGGAGGAGATGATGGCCAAGGAGGAGGAGCTGGTGAAGGTCAAGAGAGAAGCAGCTGGCTGCGGAGACA
GGTCAATGGAGATGGAGACGCTGCAGTCTCAGCTCATGGCAGAGAAATTGCAGCTGCAGGAGCAGCTCCAGGCA
GAAACCGAGCTGTGTGCCGAGGCTGAGGAGCTCCGGGCGCCGCTGACCGCCAAGAGCAGGAATTAGAAGAGAT
CTGCCATGACCTAGAGGCCAGGGTGGAGGAGGAGGAGGAGCGCTACCAGCACCTGCAGGCGGAGAAGAAGA
TGCAGCAGAACATCCAGGAGCTTGAGGAGCAGCTGGAGGAGGAGGAGAGCGCTACCAGCACCTGCAGGCGGAGAAGAAGA
AAGGTGACCACCGAGGCGAAGCTGAAAAGCTGGAGGAGGAGCAGATCATCTGGAGGACCAGAAGTGAAGCT
GGCCAAGGAAAAGAACTGCTGGAAGACAGAATAGCTGAGTTCAACACCAACCTCACAGAAGAGGAGGAGAAAT
CTAAGAGCCTCGCCAAGCTCAAGAACAGCATGAGGCAATGATCACTGACTTGGAAGAGCGCCTCCGCGAGGAG
GAGAAGCAGCGACAGGAGCTGGAGAAGACCCCGCGGAAGCTGGAGGAGAGACTCCACAGACCTCAGCGACCAGAT
CGCCGAGCTCCAGGCCAGATCGCGGAGCTCAAGATGCAGCTGGCCAAAGAAAGAGGAGGAGCTCCAGGCCGCCC
TGGCCAGAGTGGAAGAGGAAGCTGCCAGAAGACATGGCCCTCAAGAAAGATCCGGGAGCTGGAATCTCAGATC
TCTGAAGCTCCAGGAAGACCTGGAGTCTGAGCGTGCTTCCAGGAATAAAGCTGAGAAGCAGAAACGGGACCTTGG
GGAAGAGCTAGAGGCGCTGAAAACAGAGTTGGAGGACACGCTGGATTCCACAGCTGCCAGCAGGAGCTCAGGT
CAAAACGTGAGCAGGAGGTGAACATCCTGAAGAAGACCTGGAGGAGGAGGCCAAGACCCACGAGGCCAGATC
CAGGAGATGAGGCAGAAGCACTCACAGGCCGTGGAGGAGCTGGCGGAGCAGCTGGAGCAGACGAAGCGGGTGAA
AGCAAACCTCGAGAAGGCAAAGCAGACTCTGGAGAACGAGCGGGGGGAGCTGGCCAACGAGGTGAAGGTGCTGC
TGCAGGGCGGAAGGGACTCGGAGCACAAGCGCAAGAAAGTGGAGGCGCAGCTGCAGGAGCTGCAGGTCAAGTTC
AACGAGGGAGAGCGGGTGCGCACAGAGCTGGCCGACAAGGTACCAAGCTGCAGGTGGAGCTGGACAACGTGAC
CGGGCTTCTCAGCCAGTCCGACAGCAAGTCCAGCAAGCTCACCAAGGACTTCTCCGCGCTGGAGTCCAGCTGC
AGGACACTCAGGAGCTGCTGCAGGAGGAGAACCGGCAGAAGCTGAGCCTGAGCACCAAGCTCAAGCAGGTGGAG
GACGAGAAGAATTCTTCCGGGAGCAGCTGGAGGAGGAGGCCAAGCACAACTGGAGAAGCAGATCGCCAC
CCTCCATGCCAGGTGGCCGACATGAAAAGAAGATGGAGGACAGTGTGGGGTGCTTGGAACTGCTGAGGAGG
TGAAGAGGAAGCTCCAGAAGGACCTGGAGGGCTGAGCCAGCGGCACGAGGAGAAGGTGGCCGCTACGACAAG
CTGGAGAAGACCAAGACGCGGCTGCAGCAGGAGCTGGACGACCTGCTGGTGGACCTGGACCACAGCGCCAGAG
CGCGTGCAACCTGGAGAAGAAGCAGAAGAAGTTTGACCAGCTCCTGGCGGAGGAGAAGACCATCTCTGCCAAGT
ATGCAGAGGAGCGCGACCGGGCTGAGGCGGAGGCCGAGAGAAGGAGACCAAGGCTCTGTCTGCTGGCCCGGCC
CTGGAGGAAGCCATGGAGCAGAAGGCGGAGCTGGAGCGGCTCAACAAGCAGTTCCGACAGGAGATGGAGGACCT
TATGAGCTCCAAGGATGATGTGGGCAAGAGTGTCCACGAGCTGGAGAAGTCCAAGCGGGCCCTAGAGCAGCAGG
TGGAGGAGATGAAGACGCGAGCTGGAAGAGCTGGAGGACGAGCTGCAGGCCACCGAAGATGCCAAGCTGCGGTTG
GAGGTCAACCTGCAGGCCATGAAGGCCAGTTTCGAGCGGGACCTGCAGGGCCGGGACGAGCAGAGCGAGGAGAA
GAAGAAGCAGCTGGTTCAGACAGGTGCGGGAGATGGAGGCAGAGCTGGAGGACGAGAGGAAGCAGCGCTCGATGG
CAGTGGCGGCGCGAAGAAGCTGGAGATGGACCTGAAGGACCTGGAGGCGCACATCGACTCGGCCAACAGAAGC
CGGGACGAAGCCATCAAACAGCTGCGGAAGCTGCAGGCCAGATGAAGGACTGCATGCGCGAGCTGGATGACAC
CCGCGCTCTCGTGAGGAGATCCTGGCCAGGCCAAAGAGAACGAGAAGAAGCTGAAGAGCATGGAGGCCGAGA
TGATCCAGTTGCAGGAGGAAGTGGCAGCCGCGGAGCGTGCCAAGCGCCAGGCCAGCAGGAGCGGGATGAGCTG
GCTGACGAGATCGCCAACAGCAGCGGCAAAGGAGCCCTGGCGTTAGAGGAGAAGCGGCGCTTGGAGGCCCGCAT
CGCCAGCTGGAGGAGGAGCTGGAGGAGGAGCAGGGCAACACGAGCTGATCAACGACCGGCTGAAGAAGGCCA
ACCTGCAGATCGACCAGATCAACGCCGACCTGAACCTGGAGCGCGGCACGCCCAGAAGAAGCAGAAATGCTCGG


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CAGCAGCTGGAACGCCAGAACAAGGAGCTTAAGGTCAAGCTGCAGGAGATGGAGGGCACTGTCAAGTCCAAGTA
CAAGGCCCTCCATCACC GCCCTCGAGGCCAAGATTGCACAGCTGGAGGAGCAGCTGGACAACGAGACCAAGGAGC
GCCAGGCAGCCTGCAAACAGGTGCGTCGGACCGAGAAGAAGCTGAAGGATGTGCTGCTGCAGGTGGATGACGAG
CGGAGGAACGCCGAGCAGTACAAGGACCAGGCCGACAAGGCATCTACCCGCCTGAAGCAGCTCAAGCGGCAGCT
GGAGGAGGCCGAAGAGGAGGCCAGCGGGCCAACGCCTCCCGCCGAAACTGCAGCGCGAGCTGGAGGACGCCA
CTGAGACGGCCGATGCCATGAACCGCGAAGTCAGCTCCCTAAAGAACAAGCTCAGGCGCGGGGACCTGCCGTTT
GTCGTGCCCCGCCGAATGGCCCGGAAAGGCGCCGGGGATGGCTCCGACGAAGAGGTAGATGGCAAAGCGGATGG
GGCTGAGGCCAAACCTGCCGAATAAGCCTCTTCTCCTGCAGCCTGAGATGGATGGACAGACAGACACCACAGCC
TCCCCCTTCCCAGACCCCGCAGCACGCCTCTCCCCACCTTCTTGGGACTGCTGTGAACATGCCTCCTCCTGCCCT
CCGCCCCGTCCCCCATCCCGTTTCCCTCCAGGTGTTGTTGAGGGCATTGTTGCTTCTCTGCTGCATCCCCCTTC
CAGCTCCCTCCCCCTGCTCAGAATCTGATACCAAAGAGACAGGGCCCGGGCCAGGCAGAGAGCGACCAGCAGGCT
CCTCAGCCCTCTCTTGCCAAAAAGCACAAAGATGTTGAGGCGAGCAGGGCAGGCCCCCGGGGAGGGCAGAGTTTT
CTATGAATCTATTTTTCTTCAGACTGAGGCCTTTTGGTAGTCGGAGCTCCCCCAGTCGTCAGCCTCCCTGACGT
CTGCCACCAGCGCCCCCACTCCTCCTCCTTTCTTTGCTGTTTGAATCACACGTGGTGACCTCACACACCTCT
GCCCTTGGGCCTCCCACCTCCATGGCTCTGGGCGGTCAGAAGGAGCAGGCCTGGGCTCCACCTCTGTGCAGGGC
ACAGAAGGCTGGGGTGGGGGAGGAGTGGATTCTCTCTACCTGTCCCAGCAGCGCCACTGTGCTGTCTCCTCT
GATTCTAAATGTCTCAAGTGCAATGCCCCCTCCCTCCTTTACCGAGGACAGCCTGCCTCTGCCACAGCAAGG
CTGTGCGGGTCAAGCTGGAAAGGCCAGCAGCCTTCCAGTGGCTTCTCCCGAACACTCTTGGGGACCAAATATAC
TTAATGGTTAAGGGACTTGTCCCAAGTCTGACAGCCAGAGCGTTAGAGGGGCCAGCGGCTCCCCAGGCGATCTT
GTGTCTACTCTAGGACTGGGCCCCGAGGGTGGTTTACCTGCACCGTTGACTCAGTATAGTTTTAAAAATCTGCCAC
CTGCACAGGTATTTTTGAAAGCAAATAAGGTTTTCTTTTTTCCCCTTTCTTGTAATAAATGATAAAATTCCGA
GTCTTTCTCACTGCCTTTGTTTAGAAGAGAGTACTCGTCCTCACTGGTCTACACTGGTTGCCGAATTTACTTGT
ATTCCCTAACTGTTTGTATATGCTGCATTGAGACTTACGGGCAAGAAGGGCATTTTTTTTTTTTTAAAGGAAACA
AACTCTCAAATCATGAAGTGATATAAAAGCTGCATATGCCTACAAAGCTCTGAATTCAGGTCCCAGTTGCTGTC
ACAAAGGAGTGAGTGAAAACACCCACCC1TACCCCTTTTTTATATAATAAAAGTGCCTTAGCATGTGTTGCAGC
TGTCACCACTACAGTAAGCTGGTTTACAGATGTTTTCCACTGAGCATCACAATAAAGAGAACCATGTGCT

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The sequence of NOV11 was derived by laboratory cloning of cDNA fragments covering the full length and/or part of the DNA sequence of the invention, and/or by *in silico* prediction of the full length and/or part of the DNA sequence of the invention from public human sequence databases.

The cDNA coding for the NOV11 sequence was cloned by the polymerase chain reaction (PCR). PCR primers were designed based on *in silico* predictions of the full length or some portion (one or more exons) of the cDNA/protein sequence of the invention. The DNA sequence and protein sequence for a novel myosin heavy chain-like gene were obtained by exon linking, or SeqCallingTM Technology and are reported here as NOV11. These primers and methods used to amplify NOV11 cDNA are described in Example 2.

The NOV11 polypeptide (SEQ ID NO:36) encoded by SEQ ID NO:35 is 1959 amino acid residues in length and is presented using the one-letter amino acid code in Table 11B. The SignalP, Psort and/or Hydropathy results predict that NOV11 has no known signal peptide and is likely to be localized at the nucleus with a certainty of 0.9600. In alternative embodiments, a NOV11 polypeptide is located to the microbody (peroxisome) with a certainty of 0.3000, the

mitochondrial matrix space with a certainty of 0.1000, or the lysosome (lumen) with a certainty of 0.1000.

Table 11B. Encoded NOV11 Protein Sequence (SEQ ID NO:36)

MAQQAADKYLVDKNFINNPLAQADWAAKKLVWVPSDKSGFEPASLKEEVGEEAIVELVENGKKVKVNKDDIQKM
 NPPKFSKVEDMAELTCLNEASVLHNLKERYYSGLIYYSGLFCVVINPYKNLPYSEEIVEMYKGKKRHEMPPHI
 YAITDTAYRSMQDREDQSILCTGESGAGKTENTKKVIQYLAYVASSHKSCKDQGELEKQLQANPILAEFGNAK
 TVKNDNSSRFGKFIRINFDVNGYIVGANIETYLLEKSRAIRQAKEERTFHI FYLLSGAGEHLKTDLLLEPYNKY
 RFLSNGHVTIPGQQDKDMFQETMEAMRIMGIPPEEQMGLLRVISGVLQLGNI VFKKERNTDQASMPDNTAAQKVS
 HLLGINVDTFTRGILTPRIKVGRDYVQKAQTKAQDAFAEALAKATYERMFRWLVRINKALDKTKRQASFIGI
 LDIAGFEIFDLNSFEQLCINYTNEKLQQLFNHTMFILEQEYQREGIEWNFIDFGLDLQPCIDLIEKPAGPPGIL
 ALLDEECWFPKATDKSFVEKVMQEQGTHPKFQKPKQLKDKADFCI IHYAGKVDYKADEWLMKNMDPLNDNIATLL
 HQSSDKFVSELWKDVDRIIGLDQVAGMSETALPGAFKTRKGMFRFTVGQLYKEQLAKLMATLRNTNPNFVRCIIPN
 HEKKAGKLDPHLVLDQLRCNGVLEGIRICRQGFNRRVVFQEFQRQRYEILTPNSIPKGFMDGKQACVLMIKALELD
 SNLYRIGQSKVFFRAGVLAHLEERDLKITDVIIGFQACCRGYLARKAFARQQQLTAMKVLQRNCAAYLKLNRW
 QWRLFTKVKPLLQVSRQEEMMAKEEELVKVREKQLAAENRLMEMETLQSQLMAEKLQLEQLQAELELCAEAE
 ELRLRLTAKKQEELEIICHDLARVEEEERYQHQAEEKKMQQNIQEELEEEESARQKLQLEKVTTEAKLKK
 LEEEQIILEDQNCLEKLEEDRIAEFTTNLTETEEKSKSLAKLKNKHEAMITDLEERLRREEKQROELEKTR
 RKLEGDSTDLSDQIAELQAQIAELKMQLAKEEELQAALARVEEEAAQKNMALKKIRELESQISELQEDLESERA
 SRNKAQKQKRDLEGELEALKTELEDTLDTAAQQLRSKREQEVNLIKKTLEEEAKTHEAQIQEMRQKHSQAVEE
 LAEQLEQTKRVKANLEKAKQTLNERGELANEVVKVLLQGGRDSEHKRKKVEAQLOELQVKNFNEGERVTELADKV
 TKLQVELDNVTGLLSQSDSKSKLTKDFSALSQLQDTQELLQEEENRQKLSLSTKLQVEDEKNSFREQLLEEEEA
 KHNLEKQIATLHAQVADMKKKMEDSVGCLETAEEVKRLQKDLGLELSQRHEEKVAAYDKLEKTKTRLQOELDDL
 VDLDHQRQSACNLEKKQKQKFDQLLAEKTIISAKYAEERDRAEAEAREKETKALSLARALEEAMEQKAELERLNKQ
 FRTEMEDLMSSKDDVGKSVHELEKSKRALEEQVEEMKTQLELEDELEQATEDAKLRLEVNLAQMAKQAFERDLQGR
 DEQSEKKKQLVRQVREMEAELEDERKQORMAVAAARKKLEMDLKDLEAHIDSANKNRDEAIKQLRKLQAQMKDCM
 RELDDTRASREEILAQAKENEKCLKSMEAEMIQLQEELAAERAKRQAQQRERDELADEIANSSGKGALALEEKRR
 LEARIAQLEEELEEEQGNTELINDRLKKNLQIDQINADNLERGHQAQKNENARQQLERQNKELKVKLQEMEGTV
 KSKYKASITALEAKIAQLEEQLDNETKERQAACKQVRRTEKKLDVLLQVDDERRNAEQYKDQADKASTRLKQLK
 RQLEEEAEEEAQRANASRRKLQRELEDATETADAMNREVSSLKNKLRRGDLFPVVPRRMARKGAGDGSDEEVDGKA
 DGAEAKPAE

5 SNP variants of NOV11 are disclosed in Example 3.

The amino acid sequence of NOV11 has high homology to other proteins as shown in Table 11C.

Table 11C. BLASTX Results from Patp Database for NOV11

Sequences Producing High-Scoring Segment Pairs:		High Score	Smallest Sum Prob P (N)
patp:AAM78854	Human protein	9773	0.0
patp:AAM79838	Human protein	9760	0.0
patp:AAM40999	Human polypeptide	7760	0.0
patp:AAM41000	Human polypeptide	7760	0.0
patp:AAW00024	Smooth muscle myosin heavy chain SM1 isoform protein - Mus musculus	7619	0.0

In a search of sequence databases, it was found, for example, that the NOV11 nucleic acid sequence of this invention has 5116 of 5122 bases (99%) identical to a gb:GENBANK-ID:HUMMYONM|acc:M31013.1 mRNA from Homo sapiens (Human nonmuscle myosin heavy chain (NMHC) mRNA, 3' end). Further, the full amino acid sequence of the disclosed protein of the invention was found to have 1953 of 1960 amino acid residues (99%) identical to, and 1953 of 1960 amino acid residues (99%) similar to, the 1960 amino acid residue ptmr:SWISSPROT-ACC:P35579 protein from Homo sapiens (Human) (MYOSIN HEAVY CHAIN, NONMUSCLE TYPE A (CELLULAR MYOSIN HEAVY CHAIN, TYPE A) (NMMHC-A)).

Additional BLASTP results are shown in Table 11D.

Table 11D. NOV11 BLASTP Results					
Gene Index/ Identifier	Protein/Organism	Length of aa	Identity (%)	Positives (%)	Expect Value
A61231	myosin heavy chain nonmuscle form A - human	1961	1955/1961 (99%)	1956/1961 (99%)	0.0
P35579	Myosin heavy chain, nonmuscle type A (Cellular myosin heavy chain, type A) (Nonmuscle myosin heavy chain-A) (NMMHC- A) - Homo sapiens (Human)	1960	1953/1960 (99%)	1953/1960 (99%)	0.0
Q62812	Myosin heavy chain, nonmuscle type A (Cellular myosin heavy chain, type A) (Nonmuscle myosin heavy chain-A) (NMMHC- A) - Rattus norvegicus (Rat)	1961	1879/1961 (95%)	1916/1961 (97%)	0.0
P14105	Myosin heavy chain, nonmuscle (Cellular myosin heavy chain) (NMMHC) - Gallus gallus (Chicken)	1959	1813/1959 (92%)	1892/1959 (96%)	0.0
Q63731	NEURONAL MYOSIN HEAVY CHAIN - Rattus norvegicus(Rat)	1999	1781/1951 (91%)	1838/1951 (94%)	0.0

A multiple sequence alignment is given in Table 11E in a ClustalW analysis comparing NOV11 with related protein sequences disclosed in Table 11D.

Table 11E. ClustalW Analysis of NOV11

5	1. SEQ ID NO.: 36	NOV11	4. SEQ ID NO.: 105	Q62812
	2. SEQ ID NO.: 103	A61231	5. SEQ ID NO.: 106	P14105
	3. SEQ ID NO.: 104	P35579	6. SEQ ID NO.: 107	Q63731
10	NOV11	MAQQAADKYLVDKNFINNPLAQADWAAKLVWVPSDKSGFEPASLKEEVGEEAIVELVE	60	
	A61231	MAQQAADKYLVDKNFINNPLAQADWAAKLVWVPSDKSGFEPASLKEEVGERGHVELVE	60	
	P35579	MAQQAADKYLVDKNFINNPLAQADWAAKLVWVPSDKSGFEPASLKEEVGEEAIVELVE	60	
	Q62812	MAQQAADKYLVDKNFINNPLAQADCGAKLVWVPSDKSGFEPASLKEEVGEEAIVELVE	60	
	P14105	MAQRDADKYLVDKNFINNPLAQADWAAKLVWVPSDKSGFEPASLKEEVGEEAIVELVE	60	
	Q63731	MAQRDADKYLVDKNFINNPLAQADWAAKLVWVPSDKSGFEPASLKEEVGDEAIVELAE	60	
15	NOV11	NGKKVKVNKDDIQMNPPEKSKVEDMAELTCLNEASVLHNLKERYYSGLIYTYSGLFCVV	120	
	A61231	NGKKVKVNKDDIQMNPPEKSKVEDMAELTCLNEASVLHNLKERYYSGLIYTYSGLFCVV	120	
	P35579	NGKKVKVNKDDIQMNPPEKSKVEDMAELTCLNEASVLHNLKERYYSGLIYTYSGLFCVV	120	
	Q62812	NGKKVKVNKDDIQMNPPEKSKVEDMAELTCLNEASVLHNLKERYYSGLIYTYSGLFCVV	120	
20	P14105	NGKKVKVNKDDIQMNPPEKSKVEDMAELTCLNEASVLHNLKERYYSGLIYTYSGLFCVV	120	
	Q63731	NGKKVKVNKDDIQMNPPEKSKVEDMAELTCLNEASVLHNLKERYYSGLIYTYSGLFCVV	120	
25	NOV11	INPYKNLPPIYSEIIVEMYKGKKRHEMPPHIYAITDTAYRSMMQDREDQSILCTGESGAGK	180	
	A61231	INPYKNLPPIYSEIIVEMYKGKKRHEMPPHIYAITDTAYRSMMQDREDQSILCTGESGAGK	180	
	P35579	INPYKNLPPIYSEIIVEMYKGKKRHEMPPHIYAITDTAYRSMMQDREDQSILCTGESGAGK	180	
	Q62812	INPYKNLPPIYSEIIVEMYKGKKRHEMPPHIYAITDTAYRSMMQDREDQSILCTGESGAGK	180	
	P14105	INPYKNLPPIYSEIIVEMYKGKKRHEMPPHIYAITDTAYRSMMQDREDQSILCTGESGAGK	180	
	Q63731	INPYKNLPPIYSEIIVEMYKGKKRHEMPPHIYAITDTAYRSMMQDREDQSILCTGESGAGK	180	
30	NOV11	TENTKKVIOYLAVVASSHKSCKDQGELERQLLOANPILEAFGNAKTVKNDNSSRFGKFIR	240	
	A61231	TENTKKVIOYLAVVASSHKSCKDQGELERQLLOANPILEAFGNAKTVKNDNSSRFGKFIR	240	
	P35579	TENTKKVIOYLAVVASSHKSCKDQGELERQLLOANPILEAFGNAKTVKNDNSSRFGKFIR	240	
	Q62812	TENTKKVIOYLAVVASSHKSCKDQGELERQLLOANPILEAFGNAKTVKNDNSSRFGKFIR	240	
	P14105	TENTKKVIOYLAVVASSHKSCKDQGELERQLLOANPILEAFGNAKTVKNDNSSRFGKFIR	240	
35	Q63731	TENTKKVIOYLAVVASSHKSCKDQGELERQLLOANPILEAFGNAKTVKNDNSSRFGKFIR	240	
40	NOV11	INFDVNGYIVGANIETYLLEKSRAIROAKEERTFHFYLLSGAGEHLKTDLLLEPYNKY	300	
	A61231	INFDVNGYIVGANIETYLLEKSRAIROAKEERTFHFYLLSGAGEHLKTDLLLEPYNKY	300	
	P35579	INFDVNGYIVGANIETYLLEKSRAIROAKEERTFHFYLLSGAGEHLKTDLLLEPYNKY	300	
	Q62812	INFDVNGYIVGANIETYLLEKSRAIROAKEERTFHFYLLSGAGEHLKTDLLLEPYNKY	300	
	P14105	INFDVNGYIVGANIETYLLEKSRAIROAKEERTFHFYLLSGAGEHLKTDLLLEPYNKY	300	
	Q63731	INFDVNGYIVGANIETYLLEKSRAIROAKEERTFHFYLLSGAGEHLKTDLLLEPYGKY	300	
45	NOV11	RFLSNGHVTIPGQQDKDMFQETMEAMRIMGIPPEEQMGLLRVISGVLQGNIVFKKERNT	360	
	A61231	RFLSNGHVTIPGQQDKDMFQETMEAMRIMGIPPEEQMGLLRVISGVLQGNIVFKKERNT	360	
	P35579	RFLSNGHVTIPGQQDKDMFQETMEAMRIMGIPPEEQMGLLRVISGVLQGNIVFKKERNT	360	
	Q62812	RFLSNGHVTIPGQQDKDMFQETMEAMRIMGIPPEEQMGLLRVISGVLQGNIVFKKERNT	360	
	P14105	RFLSNGHVTIPGQQDKDMFQETMEAMRIMGIPPEEQMGLLRVISGVLQGNIVFKKERNT	360	
	Q63731	RFLSNGHVTIPGQQDKDMFQETMEAMRIMGIPPEEQMGLLRVISGVLQGNIVFKKERNT	360	
50	NOV11	RFLSNGHVTIPGQQDKDMFQETMEAMRIMGIPPEEQMGLLRVISGVLQGNIVFKKERNT	360	
	A61231	RFLSNGHVTIPGQQDKDMFQETMEAMRIMGIPPEEQMGLLRVISGVLQGNIVFKKERNT	360	
	P35579	RFLSNGHVTIPGQQDKDMFQETMEAMRIMGIPPEEQMGLLRVISGVLQGNIVFKKERNT	360	
	Q62812	RFLSNGHVTIPGQQDKDMFQETMEAMRIMGIPPEEQMGLLRVISGVLQGNIVFKKERNT	360	
	P14105	RFLSNGHVTIPGQQDKDMFQETMEAMRIMGIPPEEQMGLLRVISGVLQGNIVFKKERNT	360	
	Q63731	RFLSNGHVTIPGQQDKDMFQETMEAMRIMGIPPEEQMGLLRVISGVLQGNIVFKKERNT	360	
55	NOV11	DQASMPDNTAAQKVSHLLGINVDTDFTRGILTPRIKVGGRDYVQKAQTKEQADFAIEALAKA	420	
	A61231	DQASMPDNTAAQKVSHLLGINVDTDFTRGILTPRIKVGGRDYVQKAQTKEQADFAIEALAKA	420	
	P35579	DQASMPDNTAAQKVSHLLGINVDTDFTRGILTPRIKVGGRDYVQKAQTKEQADFAIEALAKA	420	
	Q62812	DQASMPDNTAAQKVSHLLGINVDTDFTRGILTPRIKVGGRDYVQKAQTKEQADFAIEALAKA	420	
	P14105	DQASMPDNTAAQKVSHLLGINVDTDFTRGILTPRIKVGGRDYVQKAQTKEQADFAIEALAKA	420	
	Q63731	DQASMPDNTAAQKVSHLLGINVDTDFTRGILTPRIKVGGRDYVQKAQTKEQADFAIEALAKA	420	

5	NOV11	TYERMFRWLVLRLINKALDKTKROGASFIGILDIAGFEIFDLNSFEQLCINYTNEKLQQLF	480
	A61231	TYERMFRWLVLRLINKALDKTKROGASFIGILDIAGFEIFDLNSFEQLCINYTNEKLQQLF	480
	P35579	TYERMFRWLVLRLINKALDKTKROGASFIGILDIAGFEIFDLNSFEQLCINYTNEKLQQLF	480
	Q62812	TYERMFRWLVLRLINKALDKTKROGASFIGILDIAGFEIFDLNSFEQLCINYTNEKLQQLF	480
	P14105	TYERMFRWLVLRLINKALDKTKROGASFIGILDIAGFEIFDLNSFEQLCINYTNEKLQQLF	480
	Q63731	TYERMFRWLVLRLINKALDKTKROGASFIGILDIAGFEIFDLNSFEQLCINYTNEKLQQLF	480
10	NOV11	NHTMFILQEEYQREGIEWNFIDFGLDLQPCIDLIEKPAGPPGILALLDEECWFPKATDK	540
	A61231	NHTMFILQEEYQREGIEWNFIDFGLDLQPCIDLIEKPAGPPGILALLDEECWFPKATDK	540
	P35579	NHTMFILQEEYQREGIEWNFIDFGLDLQPCIDLIEKPAGPPGILALLDEECWFPKATDK	540
	Q62812	NHTMFILQEEYQREGIEWNFIDFGLDLQPCIDLIEKPAGPPGILALLDEECWFPKATDK	540
	P14105	NHTMFILQEEYQREGIEWNFIDFGLDLQPCIDLIEKPAGPPGILALLDEECWFPKATDK	540
	Q63731	NHTMFILQEEYQREGIEWNFIDFGLDLQPCIDLIEKPAGPPGILALLDEECWFPKATDK	539
15	NOV11	SFVEKVMQEQGTHPKFQKPKQLKDKADFCIIHYAGKVDYKADEWLMKNMDPLNDNIATLL	600
	A61231	SFVEKVMQEQGTHPKFQKPKQLKDKADFCIIHYAGKVDYKADEWLMKNMDPLNDNIATLL	600
	P35579	SFVEKVMQEQGTHPKFQKPKQLKDKADFCIIHYAGKVDYKADEWLMKNMDPLNDNIATLL	600
	Q62812	SFVEKVMQEQGTHPKFQKPKQLKDKADFCIIHYAGKVDYKADEWLMKNMDPLNDNIATLL	600
	P14105	SFVEKVMQEQGTHPKFQKPKQLKDKADFCIIHYAGKVDYKADEWLMKNMDPLNDNIATLL	600
	Q63731	SFVEKVMQEQGTHPKFQKPKQLKDKADFCIIHYAGKVDYKADEWLMKNMDPLNDNIATLL	599
20	NOV11	HQSSDKFVSELWKDVDRIIIGLDQVAGMSETALPGAFKTRKGMFRTVGQLYKEQLAKLMAT	660
	A61231	HQSSDKFVSELWKDVDRIIIGLDQVAGMSETALPGAFKTRKGMFRTVGQLYKEQLAKLMAT	660
	P35579	HQSSDKFVSELWKDVDRIIIGLDQVAGMSETALPGAFKTRKGMFRTVGQLYKEQLAKLMAT	660
	Q62812	HQSSDKFVSELWKDVDRIIIGLDQVAGMSETALPGAFKTRKGMFRTVGQLYKEQLAKLMAT	660
	P14105	HQSSDKFVSELWKDVDRIIIGLDQVAGMSETALPGAFKTRKGMFRTVGQLYKEQLAKLMAT	660
	Q63731	HQSSDKFVSELWKDVDRIIIGLDQVAGMSETALPGAFKTRKGMFRTVGQLYKEQLAKLMAT	659
25	NOV11	LRNTNPNFVRCIIPNHEKKAGKLDPHLVLDQLRCNGVLEGIRICRQGFPPNRVVFQEFQROR	720
	A61231	LRNTNPNFVRCIIPNHEKKAGKLDPHLVLDQLRCNGVLEGIRICRQGFPPNRVVFQEFQROR	720
	P35579	LRNTNPNFVRCIIPNHEKKAGKLDPHLVLDQLRCNGVLEGIRICRQGFPPNRVVFQEFQROR	720
	Q62812	LRNTNPNFVRCIIPNHEKKAGKLDPHLVLDQLRCNGVLEGIRICRQGFPPNRVVFQEFQROR	720
	P14105	LRNTNPNFVRCIIPNHEKKAGKLDPHLVLDQLRCNGVLEGIRICRQGFPPNRVVFQEFQROR	720
	Q63731	LRNTNPNFVRCIIPNHEKKAGKLDPHLVLDQLRCNGVLEGIRICRQGFPPNRVVFQEFQROR	719
30	NOV11	YEILTPNSIPKGFMDGKQACVLMIKALELDSNLYRIGQSKVFFRAGVLAHLEEEERDLKIT	780
	A61231	YEILTPNSIPKGFMDGKQACVLMIKALELDSNLYRIGQSKVFFRAGVLAHLEEEERDLKIT	780
	P35579	YEILTPNSIPKGFMDGKQACVLMIKALELDSNLYRIGQSKVFFRAGVLAHLEEEERDLKIT	780
	Q62812	YEILTPNSIPKGFMDGKQACVLMIKALELDSNLYRIGQSKVFFRAGVLAHLEEEERDLKIT	780
	P14105	YEILTPNSIPKGFMDGKQACVLMIKALELDSNLYRIGQSKVFFRAGVLAHLEEEERDLKIT	780
	Q63731	YEILTPNSIPKGFMDGKQACVLMIKALELDSNLYRIGQSKVFFRAGVLAHLEEEERDLKIT	779
35	NOV11	DVIIGFQACCRGYLARKAFARQQQLTAMKVLQRNCAAYLKLNRWQWWRLFTKVKPLQV	840
	A61231	DVIIGFQACCRGYLARKAFARQQQLTAMKVLQRNCAAYLKLNRWQWWRLFTKVKPLQV	840
	P35579	DVIIGFQACCRGYLARKAFARQQQLTAMKVLQRNCAAYLKLNRWQWWRLFTKVKPLQV	840
	Q62812	DVIIGFQACCRGYLARKAFARQQQLTAMKVLQRNCAAYLKLNRWQWWRLFTKVKPLQV	840
	P14105	DVIIGFQACCRGYLARKAFARQQQLTAMKVLQRNCAAYLKLNRWQWWRLFTKVKPLQV	840
	Q63731	DVIIGFQACCRGYLARKAFARQQQLTAMKVLQRNCAAYLKLNRWQWWRLFTKVKPLQV	839
40	NOV11	SRQEEEMMAKEEELVKVREKQLAAENRLMEMETLQSQLMAEKLQEQQLQAE TELCAEAE	900
	A61231	SRQEEEMMAKEEELVKVREKQLAAENRLMEMETLQSQLMAEKLQEQQLQAE TELCAEAE	900
	P35579	SRQEEEMMAKEEELVKVREKQLAAENRLMEMETLQSQLMAEKLQEQQLQAE TELCAEAE	900
	Q62812	SRQEEEMMAKEEELVKVREKQLAAENRLMEMETLQSQLMAEKLQEQQLQAE TELCAEAE	900
	P14105	SRQEEEMMAKEEELVKVREKQLAAENRLMEMETLQSQLMAEKLQEQQLQAE TELCAEAE	900
	Q63731	SRQEEEMMAKEEELVKVREKQLAAENRLMEMETLQSQLMAEKLQEQQLQAE TELCAEAE	899

NOV11 ELRRLTAKKQEELEEEI CHDLEARVEEEEEERY OHLOAEKKKMQQNIQELEEQLLEEEESARO 960
A61231 ELRRLTAKKQEELEEEI CHDLEARVEEEEEERY OHLOAEKKKMQQNIQELEEQLLEEEESARO 960
P35579 ELRRLTAKKQEELEEEI CHDLEARVEEEEEERY OHLOAEKKKMQQNIQELEEQLLEEEESARO 960
Q62812 ELRRLTAKKQEELEEEI CHDLEARVEEEEEERY OHLOAEKKKMQQNIQELEEQLLEEEESARO 960
5 P14105 ELRRLTAKKQEELEEEI CHDLEARVEEEEEERY OHLOAEKKKMQQNIQELEEQLLEEEESARO 960
Q63731 ELRRLTAKKQEELEEEI CHDLEARVEEEEEERY OHLOAEKKKMQQNIQELEEQLLEEEESARO 960
NOV11 KLQLEKVTTEAKLKKLEEEQI ILEDONCKLAKEKKLEEDRIAFTTNLTETEEKSKSLAK 1020
A61231 KLQLEKVTTEAKLKKLEEEQI ILEDONCKLAKEKKLEEDRIAFTTNLTETEEKSKSLAK 1020
10 P35579 KLQLEKVTTEAKLKKLEEEQI ILEDONCKLAKEKKLEEDRIAFTTNLTETEEKSKSLAK 1020
Q62812 KLQLEKVTTEAKLKKLEEEQI ILEDONCKLAKEKKLEEDRIAFTTNLTETEEKSKSLAK 1020
P14105 KLQLEKVTTEAKLKKLEEEQI ILEDONCKLAKEKKLEEDRIAFTTNLTETEEKSKSLAK 1020
Q63731 KLQLEKVTTEAKLKKLEEEQI ILEDONCKLAKEKKLEEDRIAFTTNLTETEEKSKSLAK 1019
NOV11 LKNKHEAMITDLEERLRREEKQROELEKTRRKLEGDSTDLSQIAELQAQIAELKMQLAK 1080
A61231 LKNKHEAMITDLEERLRREEKQROELEKTRRKLEGDSTDLSQIAELQAQIAELKMQLAK 1080
P35579 LKNKHEAMITDLEERLRREEKQROELEKTRRKLEGDSTDLSQIAELQAQIAELKMQLAK 1080
Q62812 LKNKHEAMITDLEERLRREEKQROELEKTRRKLEGDSTDLSQIAELQAQIAELKMQLAK 1080
P14105 LKNKHEAMITDLEERLRREEKQROELEKTRRKLEGDSTDLSQIAELQAQIAELKMQLAK 1080
20 Q63731 LKNKHEAMITDLEERLRREEKQROELEKTRRKLEGDSTDLSQIAELQAQIAELKMQLAK 1079
NOV11 KEEELQAALARVEEEAAQKNMALKKIRELESQISELQEDLESERASRNKAQKQKRDLGEE 1140
A61231 KEEELQAALARVEEEAAQKNMALKKIRELESQISELQEDLESERASRNKAQKQKRDLGEE 1140
P35579 KEEELQAALARVEEEAAQKNMALKKIRELESQISELQEDLESERASRNKAQKQKRDLGEE 1140
25 Q62812 KEEELQAALARVEEEAAQKNMALKKIRELESQISELQEDLESERASRNKAQKQKRDLGEE 1140
P14105 KEEELQAALARVEEEAAQKNMALKKIRELESQISELQEDLESERASRNKAQKQKRDLGEE 1140
Q63731 KEEELQAALARVEEEAAQKNMALKKIRELESQISELQEDLESERASRNKAQKQKRDLGEE 1139
NOV11 LEALKTELEDITLDSTAAQOELRSKREQEVNIIKKTLEEEAKTHEAQIQEMRQKHSQAVEE 1200
A61231 LEALKTELEDITLDSTAAQOELRSKREQEVNIIKKTLEEEAKTHEAQIQEMRQKHSQAVEE 1200
30 P35579 LEALKTELEDITLDSTAAQOELRSKREQEVNIIKKTLEEEAKTHEAQIQEMRQKHSQAVEE 1200
Q62812 LEALKTELEDITLDSTAAQOELRSKREQEVNIIKKTLEEEAKTHEAQIQEMRQKHSQAVEE 1200
P14105 LEALKTELEDITLDSTAAQOELRSKREQEVNIIKKTLEEEAKTHEAQIQEMRQKHSQAVEE 1200
Q63731 LEALKTELEDITLDSTAAQOELRSKREQEVNIIKKTLEEEAKTHEAQIQEMRQKHSQAVEE 1199
NOV11 LAEQLEQTKRVKANLEKAKQTLNERGELANEVKVLLQGGDSEHKRKKVEAQLQELQVK 1260
A61231 LAEQLEQTKRVKANLEKAKQTLNERGELANEVKVLLQGGDSEHKRKKVEAQLQELQVK 1260
P35579 LAEQLEQTKRVKANLEKAKQTLNERGELANEVKVLLQGGDSEHKRKKVEAQLQELQVK 1260
40 Q62812 LAEQLEQTKRVKANLEKAKQTLNERGELANEVKVLLQGGDSEHKRKKVEAQLQELQVK 1260
P14105 LAEQLEQTKRVKANLEKAKQTLNERGELANEVKVLLQGGDSEHKRKKVEAQLQELQVK 1260
Q63731 LAEQLEQTKRVKANLEKAKQTLNERGELANEVKVLLQGGDSEHKRKKVEAQLQELQVK 1259
NOV11 FNEGERVTELADKVTKLQVELDNVTGLLSQSDSKSSKLT KDFALESQLODTQELLQEE 1320
A61231 FNEGERVTELADKVTKLQVELDNVTGLLSQSDSKSSKLT KDFALESQLODTQELLQEE 1320
45 P35579 FNEGERVTELADKVTKLQVELDNVTGLLSQSDSKSSKLT KDFALESQLODTQELLQEE 1320
Q62812 FNEGERVTELADKVTKLQVELDNVTGLLSQSDSKSSKLT KDFALESQLODTQELLQEE 1320
P14105 FNEGERVTELADKVTKLQVELDNVTGLLSQSDSKSSKLT KDFALESQLODTQELLQEE 1320
Q63731 FNEGERVTELADKVTKLQVELDNVTGLLSQSDSKSSKLT KDFALESQLODTQELLQEE 1319
NOV11 NRQKLSLSTKLQVEDEKNSFREOLEEEEE - AKHNLEKQIATLHAQVADMKKKMEDSVGC 1378
A61231 NRQKLSLSTKLQVEDEKNSFREOLEEEEE - AKHNLEKQIATLHAQVADMKKKMEDSVGC 1380
P35579 NRQKLSLSTKLQVEDEKNSFREOLEEEEE - AKHNLEKQIATLHAQVADMKKKMEDSVGC 1379
Q62812 NRQKLSLSTKLQVEDEKNSFREOLEEEEE - AKHNLEKQIATLHAQVADMKKKMEDSVGC 1380
P14105 NRQKLSLSTKLQVEDEKNSFREOLEEEEE - AKHNLEKQIATLHAQVADMKKKMEDSVGC 1379
55 Q63731 NRQKLSLSTKLQVEDEKNSFREOLEEEEE - AKHNLEKQIATLHAQVADMKKKMEDSVGC 1379
NOV11 LETAEVVRKRLQKDLGLSQRHEEKVAAYDKLEKTKTRLOQELDDLLVDLDHQRQSACNL 1438

5	A61231	LETAEEVKRKLOKDLEGLSQRHEEKVAAYDKLEKTKTRLQQEELDDLLVDLDHQRQSACNL	1440
	P35579	LETAEEVKRKLOKDLEGLSQRHEEKVAAYDKLEKTKTRLQQEELDDLLVDLDHQRQSACNL	1439
	Q62812	LETAEEAKRRLOKDLEGLSQRHEEKVAAYDKLEKTKTRLQQEELDDLLVDLDHQRQSVSNL	1440
	P14105	LETAEEAKKKLOKDLEGLSQRHEEKVAAYDKLEKTKTRLQQEELDDLLVDLDHQRQTVSNL	1439
	Q63731	LETAEEVKRKLOKDLEGLSQRHEEKVAAYDKLEKTKTRLQQEELDDLLVDLDHQRQSACNL	1439
10	NOV11	EKKQKKFDQLLAEKKTISAKYAEERDRAEAEAREKETKALSLARALEEAMEQKAELERLN	1498
	A61231	EKKQKKFDQLLAEKKTISAKYAEERDRAEAEAREKETKALSLARALEEAMEQKAELERLN	1500
	P35579	EKKQKKFDQLLAEKKTISAKYAEERDRAEAEAREKETKALSLARALEEAMEQKAELERLN	1499
	Q62812	EKKQKKFDQLLAEKKTISAKYAEERDRAEAEAREKETKALSLARALEEAMEQKAELERLN	1500
	P14105	EKKQKKFDQLLAEKKNISAKYAEERDRAEAEAREKETKALSLARALEEAMEQKAELERLN	1499
15	Q63731	EKKQKKFDQLLAEKITKSAKYAEERDRAEAEAREKETKALSLARALEEAMEQKAELERLN	1499
	NOV11	KQFRTEMEDLMSSKDDVGKSVHELEKSKRALEQQVEEMKTQLEEELEDELQATEDAKLRLE	1558
	A61231	KQFRTEMEDLMSSKDDVGKSVHELEKSKRALEQQVEEMKTQLEEELEDELQATEDAKLRLE	1560
	P35579	KQFRTEMEDLMSSKDDVGKSVHELEKSKRALEQQVEEMKTQLEEELEDELQATEDAKLRLE	1559
	Q62812	KQFRTEMEDLMSSKDDVGKSVHELEKSKRALEQQVEEMKTQLEEELEDELQATEDAKLRLE	1560
20	P14105	KQFRTEMEDLMSSKDDVGKSVHELEKSKRALEQQVEEMKTQLEEELEDELQATEDAKLRLE	1559
	Q63731	KQFRTEMEDLMSSKDDVGKSVHELEKSKRALEQQVEEMKTQLEEELEDELQATEDAKLRLE	1559
	NOV11	VNLQAMKAQFERDLQGRDEQSEEKKKQLVRQVREMEAELEDERKQORSMAVAARKKLEMDL	1618
	A61231	VNLQAMKAQFERDLQGRDEQSEEKKKQLVRQVREMEAELEDERKQORSMAVAARKKLEMDL	1620
	P35579	VNLQAMKAQFERDLQGRDEQSEEKKKQLVRQVREMEAELEDERKQORSMAVAARKKLEMDL	1619
25	Q62812	VNLQAMKAQFERDLQGRDEQSEEKKKQLVRQVREMEAELEDERKQORSMAVAARKKLEMDL	1620
	P14105	VNLQAMKAQFERDLQGRDEQSEEKKKQLVRQVREMEAELEDERKQORSMAVAARKKLEMDL	1619
	Q63731	VNLQAMKAQFERDLQGRDEQSEEKKKQLVRQVREMEAELEDERKQORSMAVAARKKLEMDL	1619
	NOV11	KDLEAHIDSANKNRDEATKQLRKLOAQMKDCMRELDTRASREEILAQAKENEKKLKSME	1678
30	A61231	KDLEAHIDSANKNRDEATKQLRKLOAQMKDCMRELDTRASREEILAQAKENEKKLKSME	1680
	P35579	KDLEAHIDSANKNRDEATKQLRKLOAQMKDCMRELDTRASREEILAQAKENEKKLKSME	1679
	Q62812	KDLEAHIDSANKNRDEATKQLRKLOAQMKDCMRELDTRASREEILAQAKENEKKLKSME	1680
	P14105	KDLEAHIDSANKNRDEATKQLRKLOAQMKDCMRELDTRASREEILAQAKENEKKLKSME	1679
	Q63731	KDLEAHIDSANKNRDEATKQLRKLOAQMKDCMRELDTRASREEILAQAKENEKKLKSME	1679
35	NOV11	AEMIQLQEELAAAERAKRQAQQRDELADEIANSSGKGALALEEKRRLEARIAQLEEELE	1738
	A61231	AEMIQLQEELAAAERAKRQAQQRDELADEIANSSGKGALALEEKRRLEARIAQLEEELE	1740
	P35579	AEMIQLQEELAAAERAKRQAQQRDELADEIANSSGKGALALEEKRRLEARIAQLEEELE	1739
	Q62812	AEMIQLQEELAAAERAKRQAQQRDELADEIANSSGKGALALEEKRRLEARIAQLEEELE	1740
	P14105	AEMIQLQEELAAAERAKRQAQQRDELADEIANSSGKGALALEEKRRLEARIAQLEEELE	1739
40	Q63731	AEMIQLQEELAAAERAKRQAQQRDELADEIANSSGKGALALEEKRRLEARIAQLEEELE	1739
	NOV11	EEQGNTELINDRLKKANLQIDQINADLNLERGHAQKNENARQQLERONKELKVKLOEMEG	1798
	A61231	EEQGNTELINDRLKKANLQIDQINADLNLERGHAQKNENARQQLERONKELKVKLOEMEG	1800
	P35579	EEQGNTELINDRLKKANLQIDQINADLNLERGHAQKNENARQQLERONKELKVKLOEMEG	1799
	Q62812	EEQGNTELINDRLKKANLQIDQINADLNLERGHAQKNENARQQLERONKELKVKLOEMEG	1800
45	P14105	EEQGNTELINDRLKKANLQIDQINADLNLERGHAQKNENARQQLERONKELKVKLOEMEG	1799
	Q63731	EEQGNTELINDRLKKANLQIDQINADLNLERGHAQKNENARQQLERONKELKVKLOEMEG	1799
50	NOV11	TVKSKYKASITALEAKIAQLEEQLDNETKERQAACKQVRRTEKKLKDVLQVDDERRNAE	1858
	A61231	TVKSKYKASITALEAKIAQLEEQLDNETKERQAACKQVRRTEKKLKDVLQVDDERRNAE	1860
	P35579	TVKSKYKASITALEAKIAQLEEQLDNETKERQAACKQVRRTEKKLKDVLQVDDERRNAE	1859
	Q62812	AVKSKYKASITALEAKIAQLEEQLDNETKERQAACKQVRRTEKKLKDVLQVDDERRNAE	1860
	P14105	AVKSKYKASITALEAKIAQLEEQLDNETKERQAACKQVRRTEKKLKDVLQVDDERRNAE	1859
55	Q63731	TVKSKYKASITALEAKIAQLEEQLDNETKERQAACKQVRRTEKKLKDVLQVDDERRNAE	1859
	NOV11	QYKDQADKASTRLKQLKQLEEEAEAEAAQRANASRRKLQRELE DATETADAMNREVSSLKN	1918
	A61231	QYKDQADKASTRLKQLKQLEEEAEAEAAQRANASRRKLQRELE DATETADAMNREVSSLKN	1920

P35579	QYKDQADKASTRLKQLKROLEEAEEEEQANASRRKLQRELE DATETADAMNREVSSLK	1919
Q62812	QYKDQADKASTRLKQLKROLEEAEEEEQANASRRKLQRELE DATETADAMNREVSSLK	1920
P14105	QYKDQADKASTRLKQLKROLEEAEEEEQANASRRKLQRELE DATETADAMNREVSSLK	1918
Q63731	QYKDQADKASTRLKQLKROLEEAEEEEQANASRRKLQRELE DATETADAMNREVSSLK	1919
NOV11	KLRRGDLPFVVPRRMARKGAGDGSDEEVDGKADGAEAKPAE	1959
A61231	KLRRGDLPFVVPRRMARKGAGDGSDEEVDGKADGAEAKPAE	1961
P35579	KLRRGDLPFVVPRRMARKGAGDGSDEEVDGKADGAEAKPAE	1960
Q62812	KLRRGDLPFVVPRRMARKGAGDGSDEEVDGKADGAEAKPAE	1961
P14105	KLRRGDLPFVVPRRMARKGAGDGSDEEVDGKADGAEAKPAE	1959
Q63731	KLRRGDLPFVVPRRMARKGAGDGSDEEVDGKADGAEAKPAE	1979
NOV11	-----	1959
A61231	-----	1961
P35579	-----	1960
Q62812	-----	1961
P14105	-----	1959
Q63731	VCGWGVEQTQGEAEVHKCRT	1999

Domain results for NOV11 were collected from the Pfam database, and then identified by the Interpro domain accession number. The results are listed in Table 11F with the statistics and domain description. These results indicate that the NOV11 polypeptide has properties similar to those of other proteins known to contain these domains.

Table 11F. Domain Analysis of NOV11

Table 11F. Domain Analysis of NOV11			
PSSMs Producing Significant Alignments		Score (bits)	E Value
myosin_head (Motor domain): domain 1 of 1, from 83 to 764		1494.5	0.0
Myosin Head	vEDmveLtyLnEpsvlhNLKkRYksdlIYTYsGlvLvsvNPYkrLpq		
NOV11	+ +++ ++ + +++++ + ++++ +++ +++++ ++ + VEDMAELTCLNEASVLHNLKERYYSGLIYTYSGLFCVVINPYKNLP-		
NOV11	iYteeiiakYrGKrryElPPHiFAiAdEAYRsMlsdkeNQsilISGESGA + +++++ + +++ + ++ + + ++++ ++++ +++ + IYSEEIVEMYKGGKRHEMPPHIYAITDTAYRSMMQDREDQSILCTGESGA		
NOV11	GKTEntKkvmqYlAaVsggnsnggeevpsvkvgvrEdqILqsNPiLEAFG ++ +++ + + +++++ + +++ ++ ++ + + GKTENTKKVIQYLAYVASSHKSK-----KDQGELERQLLQANPILEAFG		
NOV11	NAKtTrNNNSSRFGKyieIqFdktGkivGakIenYLLEKSRVvyQteger ++ + + +++ ++ + + ++ ++ + + +++ +++ + NAKTVKNDNSSRFGKFIRINFDVNGYIVGANIETYLLEKSRAIRQAKEER		
NOV11	NFHIFYQLLaGasqqnlkkeLkLtndpedYhYLnqgggevkpcytdvGidD + + + + + + + ++ + + + ++ ++ ++++ +++++ + TFHIFYLLSGAGEH-LKTDLLLE-PYNKYRFLSNGH-----VTIPGQOD		

NOV11

5

node, Lymphoid tissue, Oesophagus, Ovary, Parathyroid Gland, Peripheral Blood, Tonsils, Umbilical Vein, Whole Organism. This information was derived by determining the tissue sources of the sequences that were included in the invention including but not limited to SeqCalling sources, Public EST sources, Literature sources, and/or RACE sources.

5 The protein similarity information, expression pattern, and map location for the myosin heavy chain-like protein and nucleic acid disclosed herein suggest that this protein may have important structural and/or physiological functions characteristic of the nonmuscle myosins family. Therefore, the NOV11 nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications and as a research tool. For example, the compositions of
10 the present invention may have efficacy for treatment of patients suffering from: restenosis, neurological, glomerular diseases and other diseases, disorders and conditions of the like.

The novel nucleic acid encoding the myosin heavy chain-like protein of the invention, or fragments thereof, are useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed. These materials are further useful in the generation
15 of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. The disclosed NOV11 protein has multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, a contemplated NOV11 epitope is
20 from about amino acids 1 to 150. In another embodiment, a contemplated NOV11 epitope is from about amino acids 150 to 225. In other specific embodiments, contemplated NOV11 epitopes are from about amino acids 300 through 1950.

NOV12

25 Another NOVX protein of the invention, referred to herein as NOV12, includes three novel pancreatitis-associated protein (PAP)-like protein. The disclosed proteins have been named NOV12a, NOV12b, and NOV12c.

PAP is synthesized as a preprotein with a molecular weight of 16.6 kDa. A search of protein databases reveals marked homolgy with the carbohydrate binding region of animal lectins.
30 Although PAP has no hemagglutination activity, it does induce extensive bacterial aggregation. Further, the pattern of expression for PAP reveals that it is not found in the liver, stomach,

salivary glands, brain, kidney, or testis. Such an expression pattern correlates to a stress protein involved in the control of bacterial proliferation.

At least the NOV12a protein disclosed herein is predicted to localize extracellularly. Therefore, it is likely that this protein is accessible to a diagnostic probe, and for the various therapeutic applications described herein.

NOV12a

In one embodiment, a NOV12 variant is NOV12a (alternatively referred to herein as CG50323-01), which encodes a novel pancreatitis-associated protein (PAP)-like protein and includes the 530 nucleotide sequence (SEQ ID NO:37) shown in Table 12A. An open reading frame for the mature protein was identified beginning with an ATG codon at nucleotides 3-5 and ending with a TAA codon at nucleotides 528-530. Putative untranslated regions downstream from the termination codon and upstream from the initiation codon are underlined in Table 12A, and the start and stop codons are in bold letters.

Table 12A. NOV12a Nucleotide Sequence (SEQ ID NO:37)

```
CCATGGCCCTGCCAAGTGATCTTGGATGCTGCTTTCCTGCCTCATGCTGCTGTCTCAGGTTCAAGGTGAAGAAC
CCCAGAGGGAACTGCCCTCTGCACGGATCCGCTGTCCCAAAGGCTCCAAGGCCATGGCTCCCACTGCTATGCCT
TGTTTTTGTACCAAATCCTGGACAGATGCAGATCTGGCCTGCCAGAAGCGGCCCTCTGGAAACCTGGTGTCTG
TGCTCAGTGGGGCTGAGGGATCCTTCGTGTCTCCTGGTGAAGAGCATTGGTAACAGCTACTCATACGTCTGGA
TTGGGCTCCATGACCCACACAGGGCACCGAGCCCAATGGAGAAGGTTGGGAGTGGAGTAGCAGTGATGTGATGA
ATTACTTTGCATGGGAGAGAAATCCCTCCACCATCTCAAGCCCCGGCCACTGTGCGAGCCTGTCGAGAAGCACAG
CATTTCTGAGGTGGAAAGATTATAACTGTAATGTGAGGTTACCCATATGTCTGCAAGTTCAAATACTGGAGGCAAT
TGTA
```

The sequence of NOV12a was derived by laboratory cloning of cDNA fragments, by *in silico* prediction of the sequence. The cDNA fragments covering either the full length of the DNA sequence, or part of the sequence, or both, were cloned. *In silico* prediction was based on sequences available in CuraGen's proprietary sequence databases or in the public human sequence databases, and provided either the full length DNA sequence, or some portion thereof.

The cDNA coding for the NOV12a sequence was cloned by the polymerase chain reaction (PCR). PCR primers were designed based on *in silico* predictions of the full length or some portion (one or more exons) of the cDNA/protein sequence of the invention. The DNA sequence and protein sequence for a novel PAP-like gene were obtained by exon linking, or SeqCalling™

Technology and are reported here as NOV12a. These primers and methods used to amplify NOV12a cDNA are described in Example 2.

The NOV12a polypeptide (SEQ ID NO:38) encoded by SEQ ID NO:37 is 175 amino acid residues in length and is presented using the one-letter amino acid code in Table 12B. The SignalP, Psort and/or Hydropathy results predict that NOV12a has a signal peptide and is likely to be localized extracellularly with a certainty of 0.4896. In alternative embodiments, a NOV12a polypeptide is located to the microbody (peroxisome) with a certainty of 0.1669, the endoplasmic reticulum (membrane) with a certainty of 0.1000, or the endoplasmic reticulum (lumen) with a certainty of 0.1000.

Table 12B. Encoded NOV12a Protein Sequence (SEQ ID NO:38)

MALPSVSWMLLSCLMLLSQVQGEEPPQRELPSARIRCPKGSKAYGSHCYALFLSPKSWTDADLACQKRPSGNL
VSVLSGAEGSFVSSLVKSIGNSYSYVWIGLHDPTQGTENGEWSSSDVMNYFAWERNPSTISSPGHCAS
LSRSTAFRLRWKDYNCNVRLPYVCKFKYWRQL

NOV12b — NOV12c

In alternative embodiments, a NOV12 variant is NOV12b or NOV12c (alternatively referred to herein as 169475472 and 169475476, respectively), which include a 471 nucleotide sequence. NOV12b and NOV12c are insert assemblies that encode an open reading frame of NOV12a between residues 23 and 173. Table 12C notes the minor nucleotide and amino acid changes in NOV12b and NOV12c from the parent clone, NOV12a.

Nov No.	Alternate Reference	Change in DNA Seq. from NOV12a	Change in Protein Seq. from NOV12a
12b	169475472	A → G at bp 395	No change
12c	169475476	T → C at bp 479	No change

The sequences of NOV12b and NOV12c were derived by laboratory cloning of cDNA fragments coding for a domain of the full length form of CG50323-01 (NOV12a), between residues 23 to 173. The cDNA coding for the NOV12b and NOV12c sequences was cloned by the polymerase chain reaction (PCR). The PCR template is the previously identified plasma

(NOV12a), when available, or human cDNA. These primers and methods used to amplify NOV12b and NOV12c cDNA are described in Example 2.

SNP variants of NOV12 are disclosed in Example 3.

5 NOV12 Clones

Unless specifically addressed as NOV12a, NOV12b, or NOV12c, any reference to NOV12 is assumed to encompass all variants.

The amino acid sequence of NOV12 has high homology to other proteins as shown in Table 12D.

Table 12D. BLASTX Results from Patp Database for NOV12

Sequences Producing High-Scoring Segment Pairs:		High Score	Smallest Sum Prob P (N)
patp:AAR54098	Mouse PAP	921	3.0e-92
patp:AAR57117	Human Pancreatitis-Associated Protein	921	3.0e-92
patp:AAB43568	Human cancer associated protein	921	3.0e-92
patp:AAR14795	Fragment A3 from human pancreatitis associated protein	915	1.3e-91
patp:AAW71682	Human pancreatitis-associated protein	813	8.4e-81

In a search of sequence databases, it was found, for example, that the NOV12a nucleic acid sequence of the invention has 514 of 520 bases (98%) identical to a gb:GENBANK-

15 ID:S51768|acc:S51768.1 mRNA from Homo sapiens (PAP-H=pancreatitis-associated protein [human, pancreas, mRNA, 797 nt]). Further, the full amino acid sequence of the disclosed protein of the invention has 169 of 169 amino acid residues (100%) identical to, and 169 of 169 amino acid residues (100%) similar to, the 175 amino acid residue ptr:SWISSPROT-ACC:Q06141 protein from Homo sapiens (Human) (PANCREATITIS-ASSOCIATED PROTEIN 1
20 PRECURSOR).

Additional BLASTP results are shown in Table 12E.

Table 12E. NOV12 BLASTP Results

Gene Index/ Identifier	Protein/Organism	Length of aa	Identity (%)	Positives (%)	Expect Value
	Pancreatitis-associated		169/169	169/169	

Q06141	protein 1 precursor - Homo sapiens (Human)	175	(100%)	(100%)	3.8e-92
P23132	Lithostathine precursor (Pancreatic stone protein) (PSP) (Pancreatic thread protein) (PTP) (Islet of langerhans regenerating protein) (REG) (Islet cells regeneration factor) (ICRF) - Bos taurus (Bovine)	175	118/169 (69%)	144/169 (85%)	2.8e-66
P25031	Pancreatitis-associated protein 1 precursor (Peptide 23) (REG-2) - Rattus norvegicus (Rat)	175	117/169 (69%)	140/169 (82%)	1.9e-65
P35230	Pancreatitis-associated protein 1 precursor (REG III-beta) - Mus musculus (Mouse)	175	115/164 (70%)	135/164 (82%)	2.2e-64
P42854	Pancreatitis-associated protein 3 precursor - Rattus norvegicus (Rat)	174	117/170 (68%)	141/170 (82%)	5.3e-63

A multiple sequence alignment is given in Table 12F, with the NOV12 protein of the invention being shown in lines 1, 2, and 3, in a ClustalW analysis comparing NOV12 with related protein sequences of Table 12E.

Table 12F. ClustalW Analysis of NOV12

10	1. SEQ ID NO.: 38	NOV12a	4. SEQ ID NO.: 111	P25031
	2. SEQ ID NO.: 109	Q06141	5. SEQ ID NO.: 112	P35230
	3. SEQ ID NO.: 110	P23132	6. SEQ ID NO.: 113	P42854
15	NOV12a	-----MALPSVSWMLLSCLMLLSQVQGEPPQRELPSARIRCPKGSKAYGSHCYALEFLSPKS	56	
	Q06141	MLPPMALPSVSWMLLSCLMLLSQVQGEPPQRELPSARIRCPKGSKAYGSHCYALEFLSPKS	60	
	P23132	MLPSLGLPRLSWMLLSCLMLLSQIQGENSQRELPSARISCPSGSMAYRSHCYALEFKTPKT	60	
	P25031	MLHRLAFPVMSWMLLSCLMLLSQVQGEDSPKKIP SARISCPKGSQAYGSYCYALFQIPQT	60	
	P35230	MLPPTACSVMSWMLLSCLMLLSQVQGEDSLKNIP SARISCPKGSQAYGSYCYALFQIPQT	60	
20	P42854	MLPRVALTTMSWMLLSCLMLLSQVQGEDAKEDVETSRISCPKGSRAYGSYCYALFVSVSKS	60	
	NOV12a	WTDADLACQKRPSGNLVSVLSCAEGSFVSSLVKSI GNSYSYVWIGLHDPTQGTPEPNNGGW	116	
	Q06141	WTDADLACQKRPSGNLVSVLSCAEGSFVSSLVKSI GNSYSYVWIGLHDPTQGTPEPNNGGW	120	
	P23132	WMDADIACQKRPSGHLVSVLSCAEGSFVASLVRNNINTQSDTWIGLHDPTGSEANAGGW	120	
25	P25031	WFDADLACQKRPEGHLVSVLNVAEASFSLSMVKRTGNSYQYTWIGLHDPTLGGEPPNGGGW	120	
	P35230	WFDADLACQKRPGGHLVSVLNSAEASFSLSMVKRTGNSYQYTWIGLHDPTLGGEPPNGGGW	120	
	P42854	WFDADLACQKRPSGHLVSVLSCAEGSFVSSLVKSI GNSYSYVWIGLHDPTQGTPEPNNGGW	120	
30	NOV12a	EWSSSDVMNYFAWERNPSTISSPGHCASLSRSTAF LRWKDYN CNVRLPYVCKE KYWRQL-	175	
	Q06141	EWSSSDVMNYFAWERNPSTISSPGHCASLSRSTAF LRWKDYN CNVRLPYVCKE TD-----	175	

P23132 EWISNDVNLNYVAWEITDPAATISSPGYCGSLSRSSGYLKWDRDHNCNLNLPYVCKFTD----- 175
 P25031 EWSNNDIMNYVNWERNPSTALDRGFCGSLSRSSGFLRWDTTCEVKLPYVCKFTG----- 175
 P35230 EWSNNDVMNYFNWERNPSTALDRAFCGSLSRASGFLKWDRMTCEVKLPYVCKFTG----- 175
 P42854 EWSNADVMMNYFNWETNPSSVSG-SHCGTLIRASGFLRWRENNCISELPYVCKFKA----- 174

NOV12a - 175
 Q06141 - 175
 P23132 - 175
 P25031 - 175
 P35230 - 175
 P42854 - 174

Domain results for NOV12 were collected from the Pfam database, and then identified by the Interpro domain accession number. The results are listed in Table 12G with the statistics and domain description. These results indicate that the NOV12 polypeptides have properties similar to those of other proteins known to contain these domains.

Table 12G. Domain Analysis of NOV12

PSSMs Producing Significant Alignments		Score (bits)	E Value
lectin_c type domain: domain 1 of 1, from 53 to 169		146.5	4.5e-40
Lectin-C	esktWaeAelaCqkeghAHLvsIqsaeEqsfvvafllstltkksnty ++++ ++ +++ +++++ + +++ + + ++++++++ + +++++		
NOV12a	SPKSWTDADLACQKRPSG-NLVSVLGAEGSFVSSLVKSIGN-SYSY		
NOV12a	aWIGLtdintegtwwegwetdgspvnytenWapgePnnrgnhGgnEdCv + +++++ ++++++++ ++++++ +++++ ++ + VWIGLHDPTQGTEPNGEWESSSDVMNYFAWERNPSTISS----PGHCA		
NOV12a	eiytddtflaGkWnDepCdsklpyvCef (SEQ ID NO:114) +++++++ + + + ++ +++++ ++ SLSRSTAFL-RWKDYNCNVRLPYVCKF (SEQ ID NO:38)		

The NOV12 proteins disclosed in this invention are expressed in at least the following tissues: at very low expression level in healthy pancreas and at much higher level during the acute phase of pancreatitis; it is also expressed at high level in normal small intestine. This information was derived by determining the tissue sources of the sequences that were included in the invention including but not limited to SeqCalling sources, Public EST sources, Literature sources, and/or RACE sources.

The protein similarity information, expression pattern, and map location for the PAP-like protein and nucleic acid disclosed herein suggest that this protein may have important structural and/or physiological functions characteristic of the Lectin C family. Therefore, the NOV12 nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications and as a research tool. For example, the compositions of the present invention will have efficacy for treatment of patients suffering from: acute pancreatitis and chronic pancreatitis, and other diseases, disorders and conditions of the like.

The novel NOV12 proteins of the invention, or fragments thereof, are useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed.

These materials are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. The disclosed NOV12 protein has multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, a contemplated NOV12 epitope is from about amino acids 20 to 45. In another embodiment, a contemplated NOV12 epitope is from about amino acids 45 to 57. In other specific embodiments, contemplated NOV12 epitopes are from about amino acids 55 to 70, 72 to 77, 95 to 143, and 145 to 170.

NOVX Nucleic Acids and Polypeptides

One aspect of the invention pertains to isolated nucleic acid molecules that encode NOVX polypeptides or biologically active portions thereof. Also included in the invention are nucleic acid fragments sufficient for use as hybridization probes to identify NOVX-encoding nucleic acids (e.g., NOVX mRNAs) and fragments for use as PCR primers for the amplification and/or mutation of NOVX nucleic acid molecules. As used herein, the term "nucleic acid molecule" is intended to include DNA molecules (e.g., cDNA or genomic DNA), RNA molecules (e.g., mRNA), analogs of the DNA or RNA generated using nucleotide analogs, and derivatives, fragments and homologs thereof. The nucleic acid molecule may be single-stranded or double-stranded, but preferably is comprised double-stranded DNA.

An NOVX nucleic acid can encode a mature NOVX polypeptide. As used herein, a "mature" form of a polypeptide or protein disclosed in the present invention is the product of a

naturally occurring polypeptide or precursor form or proprotein. The naturally occurring polypeptide, precursor or proprotein includes, by way of nonlimiting example, the full-length gene product, encoded by the corresponding gene. Alternatively, it may be defined as the polypeptide, precursor or proprotein encoded by an ORF described herein. The product "mature" form arises, again by way of nonlimiting example, as a result of one or more naturally occurring processing steps as they may take place within the cell, or host cell, in which the gene product arises. Examples of such processing steps leading to a "mature" form of a polypeptide or protein include the cleavage of the N-terminal methionine residue encoded by the initiation codon of an ORF, or the proteolytic cleavage of a signal peptide or leader sequence. Thus a mature form arising from a precursor polypeptide or protein that has residues 1 to N, where residue 1 is the N-terminal methionine, would have residues 2 through N remaining after removal of the N-terminal methionine. Alternatively, a mature form arising from a precursor polypeptide or protein having residues 1 to N, in which an N-terminal signal sequence from residue 1 to residue M is cleaved, would have the residues from residue M+1 to residue N remaining. Further as used herein, a "mature" form of a polypeptide or protein may arise from a step of post-translational modification other than a proteolytic cleavage event. Such additional processes include, by way of non-limiting example, glycosylation, myristoylation or phosphorylation. In general, a mature polypeptide or protein may result from the operation of only one of these processes, or a combination of any of them.

The term "probes", as utilized herein, refers to nucleic acid sequences of variable length, preferably between at least about 10 nucleotides (nt), 100 nt, or as many as approximately, *e.g.*, 6,000 nt, depending upon the specific use. Probes are used in the detection of identical, similar, or complementary nucleic acid sequences. Longer length probes are generally obtained from a natural or recombinant source, are highly specific, and much slower to hybridize than shorter-length oligomer probes. Probes may be single- or double-stranded and designed to have specificity in PCR, membrane-based hybridization technologies, or ELISA-like technologies.

The term "isolated" nucleic acid molecule, as utilized herein, is one, which is separated from other nucleic acid molecules which are present in the natural source of the nucleic acid. Preferably, an "isolated" nucleic acid is free of sequences which naturally flank the nucleic acid (*i.e.*, sequences located at the 5'- and 3'-termini of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. For example, in various embodiments, the

isolated NOVX nucleic acid molecules can contain less than about 5 kb, 4 kb, 3 kb, 2 kb, 1 kb, 0.5 kb or 0.1 kb of nucleotide sequences which naturally flank the nucleic acid molecule in genomic DNA of the cell/tissue from which the nucleic acid is derived (*e.g.*, brain, heart, liver, spleen, etc.). Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material or culture medium when produced by recombinant techniques, or of chemical precursors or other chemicals when chemically synthesized.

A nucleic acid molecule of the invention, *e.g.*, a nucleic acid molecule having the nucleotide sequence SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37, or a complement of this aforementioned nucleotide sequence, can be isolated using standard molecular biology techniques and the sequence information provided herein. Using all or a portion of the nucleic acid sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37 as a hybridization probe, NOVX molecules can be isolated using standard hybridization and cloning techniques (*e.g.*, as described in Sambrook, *et al.*, (eds.), MOLECULAR CLONING: A LABORATORY MANUAL 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989; and Ausubel, *et al.*, (eds.), CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, New York, NY, 1993.)

A nucleic acid of the invention can be amplified using cDNA, mRNA or alternatively, genomic DNA, as a template and appropriate oligonucleotide primers according to standard PCR amplification techniques. The nucleic acid so amplified can be cloned into an appropriate vector and characterized by DNA sequence analysis. Furthermore, oligonucleotides corresponding to NOVX nucleotide sequences can be prepared by standard synthetic techniques, *e.g.*, using an automated DNA synthesizer.

As used herein, the term "oligonucleotide" refers to a series of linked nucleotide residues, which oligonucleotide has a sufficient number of nucleotide bases to be used in a PCR reaction.

A short oligonucleotide sequence may be based on, or designed from, a genomic or cDNA sequence and is used to amplify, confirm, or reveal the presence of an identical, similar or complementary DNA or RNA in a particular cell or tissue. Oligonucleotides comprise portions of a nucleic acid sequence having about 10 nt, 50 nt, or 100 nt in length, preferably about 15 nt to 30 nt in length. In one embodiment of the invention, an oligonucleotide comprising a nucleic acid molecule less than 100 nt in length would further comprise at least 6 contiguous nucleotides SEQ

ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37, or a complement thereof. Oligonucleotides may be chemically synthesized and may also be used as probes.

In another embodiment, an isolated nucleic acid molecule of the invention comprises a nucleic acid molecule that is a complement of the nucleotide sequence shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37, or a portion of this nucleotide sequence (*e.g.*, a fragment that can be used as a probe or primer or a fragment encoding a biologically-active portion of an NOVX polypeptide). A nucleic acid molecule that is complementary to the nucleotide sequence shown SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37 is one that is sufficiently complementary to the nucleotide sequence shown SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37 that it can hydrogen bond with little or no mismatches to the nucleotide sequence shown SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37 thereby forming a stable duplex.

As used herein, the term "complementary" refers to Watson-Crick or Hoogsteen base pairing between nucleotides units of a nucleic acid molecule, and the term "binding" means the physical or chemical interaction between two polypeptides or compounds or associated polypeptides or compounds or combinations thereof. Binding includes ionic, non-ionic, van der Waals, hydrophobic interactions, and the like. A physical interaction can be either direct or indirect. Indirect interactions may be through or due to the effects of another polypeptide or compound. Direct binding refers to interactions that do not take place through, or due to, the effect of another polypeptide or compound, but instead are without other substantial chemical intermediates.

Fragments provided herein are defined as sequences of at least 6 (contiguous) nucleic acids or at least 4 (contiguous) amino acids, a length sufficient to allow for specific hybridization in the case of nucleic acids or for specific recognition of an epitope in the case of amino acids, respectively, and are at most some portion less than a full length sequence. Fragments may be derived from any contiguous portion of a nucleic acid or amino acid sequence of choice. Derivatives are nucleic acid sequences or amino acid sequences formed from the native compounds either directly or by modification or partial substitution. Analogs are nucleic acid sequences or amino acid sequences that have a structure similar to, but not identical to, the native compound but differs from it in respect to certain components or side chains. Analogs may be

synthetic or from a different evolutionary origin and may have a similar or opposite metabolic activity compared to wild type. Homologs are nucleic acid sequences or amino acid sequences of a particular gene that are derived from different species.

Derivatives and analogs may be full length or other than full length, if the derivative or analog contains a modified nucleic acid or amino acid, as described below. Derivatives or analogs of the nucleic acids or proteins of the invention include, but are not limited to, molecules comprising regions that are substantially homologous to the nucleic acids or proteins of the invention, in various embodiments, by at least about 70%, 80%, or 95% identity (with a preferred identity of 80-95%) over a nucleic acid or amino acid sequence of identical size or when compared to an aligned sequence in which the alignment is done by a computer homology program known in the art, or whose encoding nucleic acid is capable of hybridizing to the complement of a sequence encoding the aforementioned proteins under stringent, moderately stringent, or low stringent conditions. *See e.g.* Ausubel, *et al.*, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, New York, NY, 1993, and below.

A "homologous nucleic acid sequence" or "homologous amino acid sequence," or variations thereof, refer to sequences characterized by a homology at the nucleotide level or amino acid level as discussed above. Homologous nucleotide sequences encode those sequences coding for isoforms of NOVX polypeptides. Isoforms can be expressed in different tissues of the same organism as a result of, for example, alternative splicing of RNA. Alternatively, isoforms can be encoded by different genes. In the invention, homologous nucleotide sequences include nucleotide sequences encoding for an NOVX polypeptide of species other than humans, including, but not limited to: vertebrates, and thus can include, *e.g.*, frog, mouse, rat, rabbit, dog, cat, cow, horse, and other organisms. Homologous nucleotide sequences also include, but are not limited to, naturally occurring allelic variations and mutations of the nucleotide sequences set forth herein. A homologous nucleotide sequence does not, however, include the exact nucleotide sequence encoding human NOVX protein. Homologous nucleic acid sequences include those nucleic acid sequences that encode conservative amino acid substitutions (see below) in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37, as well as a polypeptide possessing NOVX biological activity. Various biological activities of the NOVX proteins are described below.

An NOVX polypeptide is encoded by the open reading frame ("ORF") of an NOVX nucleic acid. An ORF corresponds to a nucleotide sequence that could potentially be translated into a polypeptide. A stretch of nucleic acids comprising an ORF is uninterrupted by a stop codon. An ORF that represents the coding sequence for a full protein begins with an ATG "start" codon and terminates with one of the three "stop" codons, namely, TAA, TAG, or TGA. For the purposes of this invention, an ORF may be any part of a coding sequence, with or without a start codon, a stop codon, or both. For an ORF to be considered as a good candidate for coding for a *bona fide* cellular protein, a minimum size requirement is often set, *e.g.*, a stretch of DNA that would encode a protein of 50 amino acids or more.

The nucleotide sequences determined from the cloning of the human NOVX genes allows for the generation of probes and primers designed for use in identifying and/or cloning NOVX homologues in other cell types, *e.g.* from other tissues, as well as NOVX homologues from other vertebrates. The probe/primer typically comprises substantially purified oligonucleotide. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12, 25, 50, 100, 150, 200, 250, 300, 350 or 400 consecutive sense strand nucleotide sequence SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37; or an anti-sense strand nucleotide sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37; or of a naturally occurring mutant of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37.

Probes based on the human NOVX nucleotide sequences can be used to detect transcripts or genomic sequences encoding the same or homologous proteins. In various embodiments, the probe further comprises a label group attached thereto, *e.g.* the label group can be a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes can be used as a part of a diagnostic test kit for identifying cells or tissues which mis-express an NOVX protein, such as by measuring a level of an NOVX-encoding nucleic acid in a sample of cells from a subject *e.g.*, detecting NOVX mRNA levels or determining whether a genomic NOVX gene has been mutated or deleted.

"A polypeptide having a biologically-active portion of an NOVX polypeptide" refers to polypeptides exhibiting activity similar, but not necessarily identical to, an activity of a polypeptide of the invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. A nucleic acid fragment encoding a "biologically-active

portion of NOVX" can be prepared by isolating a portion SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37, that encodes a polypeptide having an NOVX biological activity (the biological activities of the NOVX proteins are described below), expressing the encoded portion of NOVX protein (*e.g.*, by recombinant expression *in vitro*) and assessing the activity of the encoded portion of NOVX.

NOVX Nucleic Acid and Polypeptide Variants

The invention further encompasses nucleic acid molecules that differ from the nucleotide sequences shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37 due to degeneracy of the genetic code and thus encode the same NOVX proteins as that encoded by the nucleotide sequences shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37. In another embodiment, an isolated nucleic acid molecule of the invention has a nucleotide sequence encoding a protein having an amino acid sequence shown in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, and 38.

In addition to the human NOVX nucleotide sequences shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37, it will be appreciated by those skilled in the art that DNA sequence polymorphisms that lead to changes in the amino acid sequences of the NOVX polypeptides may exist within a population (*e.g.*, the human population). Such genetic polymorphism in the NOVX genes may exist among individuals within a population due to natural allelic variation. As used herein, the terms "gene" and "recombinant gene" refer to nucleic acid molecules comprising an open reading frame (ORF) encoding an NOVX protein, preferably a vertebrate NOVX protein. Such natural allelic variations can typically result in 1-5% variance in the nucleotide sequence of the NOVX genes. Any and all such nucleotide variations and resulting amino acid polymorphisms in the NOVX polypeptides, which are the result of natural allelic variation and that do not alter the functional activity of the NOVX polypeptides, are intended to be within the scope of the invention.

Moreover, nucleic acid molecules encoding NOVX proteins from other species, and thus that have a nucleotide sequence that differs from the human SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37 are intended to be within the scope of the invention. Nucleic acid molecules corresponding to natural allelic variants and homologues of the NOVX cDNAs of the invention can be isolated based on their homology to the human NOVX nucleic

acids disclosed herein using the human cDNAs, or a portion thereof, as a hybridization probe according to standard hybridization techniques under stringent hybridization conditions.

Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 6 nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising the nucleotide sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37. In another embodiment, the nucleic acid is at least 10, 25, 50, 100, 250, 500, 750, 1000, 1500, or 2000 or more nucleotides in length. In yet another embodiment, an isolated nucleic acid molecule of the invention hybridizes to the coding region. As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences at least 60% homologous to each other typically remain hybridized to each other.

Homologs (*i.e.*, nucleic acids encoding NOVX proteins derived from species other than human) or other related sequences (*e.g.*, paralogs) can be obtained by low, moderate or high stringency hybridization with all or a portion of the particular human sequence as a probe using methods well known in the art for nucleic acid hybridization and cloning.

As used herein, the phrase "stringent hybridization conditions" refers to conditions under which a probe, primer or oligonucleotide will hybridize to its target sequence, but to no other sequences. Stringent conditions are sequence-dependent and will be different in different circumstances. Longer sequences hybridize specifically at higher temperatures than shorter sequences. Generally, stringent conditions are selected to be about 5 °C lower than the thermal melting point (T_m) for the specific sequence at a defined ionic strength and pH. The T_m is the temperature (under defined ionic strength, pH and nucleic acid concentration) at which 50% of the probes complementary to the target sequence hybridize to the target sequence at equilibrium. Since the target sequences are generally present at excess, at T_m , 50% of the probes are occupied at equilibrium. Typically, stringent conditions will be those in which the salt concentration is less than about 1.0 M sodium ion, typically about 0.01 to 1.0 M sodium ion (or other salts) at pH 7.0 to 8.3 and the temperature is at least about 30°C for short probes, primers or oligonucleotides (*e.g.*, 10 nt to 50 nt) and at least about 60°C for longer probes, primers and oligonucleotides. Stringent conditions may also be achieved with the addition of destabilizing agents, such as formamide.

Stringent conditions are known to those skilled in the art and can be found in Ausubel, *et al.*, (eds.), CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. Preferably, the conditions are such that sequences at least about 65%, 70%, 75%, 85%, 90%, 95%, 98%, or 99% homologous to each other typically remain hybridized to each other. A non-limiting example of stringent hybridization conditions are hybridization in a high salt buffer comprising 6X SSC, 50 mM Tris-HCl (pH 7.5), 1 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.02% BSA, and 500 mg/ml denatured salmon sperm DNA at 65°C, followed by one or more washes in 0.2X SSC, 0.01% BSA at 50°C. An isolated nucleic acid molecule of the invention that hybridizes under stringent conditions to the sequences SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37, corresponds to a naturally-occurring nucleic acid molecule. As used herein, a "naturally-occurring" nucleic acid molecule refers to an RNA or DNA molecule having a nucleotide sequence that occurs in nature (*e.g.*, encodes a natural protein).

In a second embodiment, a nucleic acid sequence that is hybridizable to the nucleic acid molecule comprising the nucleotide sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37, or fragments, analogs or derivatives thereof, under conditions of moderate stringency is provided. A non-limiting example of moderate stringency hybridization conditions are hybridization in 6X SSC, 5X Denhardt's solution, 0.5% SDS and 100 mg/ml denatured salmon sperm DNA at 55°C, followed by one or more washes in 1X SSC, 0.1% SDS at 37°C. Other conditions of moderate stringency that may be used are well-known within the art. *See, e.g.*, Ausubel, *et al.* (eds.), 1993, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, NY, and Kriegler, 1990; GENE TRANSFER AND EXPRESSION, A LABORATORY MANUAL, Stockton Press, NY.

In a third embodiment, a nucleic acid that is hybridizable to the nucleic acid molecule comprising the nucleotide sequences SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37, or fragments, analogs or derivatives thereof, under conditions of low stringency, is provided. A non-limiting example of low stringency hybridization conditions are hybridization in 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 mg/ml denatured salmon sperm DNA, 10% (wt/vol) dextran sulfate at 40°C, followed by one or more washes in 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS at 50°C. Other conditions of low stringency that may be used are well known in

the art (*e.g.*, as employed for cross-species hybridizations). *See, e.g.*, Ausubel, *et al.* (eds.), 1993, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, NY, and Kriegler, 1990, GENE TRANSFER AND EXPRESSION, A LABORATORY MANUAL, Stockton Press, NY; Shilo and Weinberg, 1981. *Proc Natl Acad Sci USA* 78: 6789-6792.

5

Conservative Mutations

In addition to naturally-occurring allelic variants of NOVX sequences that may exist in the population, the skilled artisan will further appreciate that changes can be introduced by mutation into the nucleotide sequences SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37, thereby leading to changes in the amino acid sequences of the encoded NOVX proteins, without altering the functional ability of said NOVX proteins. For example, nucleotide substitutions leading to amino acid substitutions at "non-essential" amino acid residues can be made in the sequence SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, and 38. A "non-essential" amino acid residue is a residue that can be altered from the wild-type sequences of the NOVX proteins without altering their biological activity, whereas an "essential" amino acid residue is required for such biological activity. For example, amino acid residues that are conserved among the NOVX proteins of the invention are predicted to be particularly non-amenable to alteration. Amino acids for which conservative substitutions can be made are well-known within the art.

Another aspect of the invention pertains to nucleic acid molecules encoding NOVX proteins that contain changes in amino acid residues that are not essential for activity. Such NOVX proteins differ in amino acid sequence from SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37 yet retain biological activity. In one embodiment, the isolated nucleic acid molecule comprises a nucleotide sequence encoding a protein, wherein the protein comprises an amino acid sequence at least about 45% homologous to the amino acid sequences SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, and 38. Preferably, the protein encoded by the nucleic acid molecule is at least about 60% homologous to SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, and 38; more preferably at least about 70% homologous SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, and 38; still more preferably at least about 80% homologous to SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, and 38; even more preferably

at least about 90% homologous to SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, and 38; and most preferably at least about 95% homologous to SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, and 38.

An isolated nucleic acid molecule encoding an NOVX protein homologous to the protein of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, and 38 can be created by introducing one or more nucleotide substitutions, additions or deletions into the nucleotide sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37, such that one or more amino acid substitutions, additions or deletions are introduced into the encoded protein.

Mutations can be introduced into SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37 by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more predicted, non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined within the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Thus, a predicted non-essential amino acid residue in the NOVX protein is replaced with another amino acid residue from the same side chain family. Alternatively, in another embodiment, mutations can be introduced randomly along all or part of an NOVX coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for NOVX biological activity to identify mutants that retain activity. Following mutagenesis SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37, the encoded protein can be expressed by any recombinant technology known in the art and the activity of the protein can be determined.

The relatedness of amino acid families may also be determined based on side chain interactions. Substituted amino acids may be fully conserved "strong" residues or fully conserved "weak" residues. The "strong" group of conserved amino acid residues may be any one of the

following groups: STA, NEQK, NHQK, NDEQ, QHRK, MILV, MILF, HY, FYW, wherein the single letter amino acid codes are grouped by those amino acids that may be substituted for each other. Likewise, the "weak" group of conserved residues may be any one of the following: CSA, ATV, SAG, STNK, STPA, SGND, SNDEQK, NDEQHK, NEQHRK, VLIM, HFY, wherein the letters within each group represent the single letter amino acid code.

In one embodiment, a mutant NOVX protein can be assayed for (i) the ability to form protein:protein interactions with other NOVX proteins, other cell-surface proteins, or biologically-active portions thereof, (ii) complex formation between a mutant NOVX protein and an NOVX ligand; or (iii) the ability of a mutant NOVX protein to bind to an intracellular target protein or biologically-active portion thereof; (e.g. avidin proteins).

In yet another embodiment, a mutant NOVX protein can be assayed for the ability to regulate a specific biological function (e.g., regulation of insulin release).

Antisense Nucleic Acids

Another aspect of the invention pertains to isolated antisense nucleic acid molecules that are hybridizable to or complementary to the nucleic acid molecule comprising the nucleotide sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37, or fragments, analogs or derivatives thereof. An "antisense" nucleic acid comprises a nucleotide sequence that is complementary to a "sense" nucleic acid encoding a protein (e.g., complementary to the coding strand of a double-stranded cDNA molecule or complementary to an mRNA sequence). In specific aspects, antisense nucleic acid molecules are provided that comprise a sequence complementary to at least about 10, 25, 50, 100, 250 or 500 nucleotides or an entire NOVX coding strand, or to only a portion thereof. Nucleic acid molecules encoding fragments, homologs, derivatives and analogs of an NOVX protein of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 29, and 31, or antisense nucleic acids complementary to an NOVX nucleic acid sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37, are additionally provided.

In one embodiment, an antisense nucleic acid molecule is antisense to a "coding region" of the coding strand of a nucleotide sequence encoding an NOVX protein. The term "coding region" refers to the region of the nucleotide sequence comprising codons which are translated into amino acid residues. In another embodiment, the antisense nucleic acid molecule is antisense to a

"noncoding region" of the coding strand of a nucleotide sequence encoding the NOVX protein. The term "noncoding region" refers to 5' and 3' sequences which flank the coding region that are not translated into amino acids (*i.e.*, also referred to as 5' and 3' untranslated regions).

Given the coding strand sequences encoding the NOVX protein disclosed herein, antisense
 5 nucleic acids of the invention can be designed according to the rules of Watson and Crick or Hoogsteen base pairing. The antisense nucleic acid molecule can be complementary to the entire coding region of NOVX mRNA, but more preferably is an oligonucleotide that is antisense to only a portion of the coding or noncoding region of NOVX mRNA. For example, the antisense oligonucleotide can be complementary to the region surrounding the translation start site of
 10 NOVX mRNA. An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 nucleotides in length. An antisense nucleic acid of the invention can be constructed using chemical synthesis or enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (*e.g.*, an antisense oligonucleotide) can be chemically synthesized using naturally-occurring nucleotides or variously modified nucleotides designed to
 15 increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids (*e.g.*, phosphorothioate derivatives and acridine substituted nucleotides can be used).

Examples of modified nucleotides that can be used to generate the antisense nucleic acid include: 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine,
 20 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxycarboxymethyl-2-thiouracil,
 25 beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the
 30 antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an antisense orientation (*i.e.*, RNA transcribed from the

inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest, described further in the following subsection).

The antisense nucleic acid molecules of the invention are typically administered to a subject or generated *in situ* such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding an NOVX protein to thereby inhibit expression of the protein (*e.g.*, by inhibiting transcription and/or translation). The hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule that binds to DNA duplexes, through specific interactions in the major groove of the double helix. An example of a route of administration of antisense nucleic acid molecules of the invention includes direct injection at a tissue site. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then administered systemically. For example, for systemic administration, antisense molecules can be modified such that they specifically bind to receptors or antigens expressed on a selected cell surface (*e.g.*, by linking the antisense nucleic acid molecules to peptides or antibodies that bind to cell surface receptors or antigens). The antisense nucleic acid molecules can also be delivered to cells using the vectors described herein. To achieve sufficient nucleic acid molecules, vector constructs in which the antisense nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

In yet another embodiment, the antisense nucleic acid molecule of the invention is an α -anomeric nucleic acid molecule. An α -anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual β -units, the strands run parallel to each other. *See, e.g.*, Gaultier, *et al.*, 1987. *Nucl. Acids Res.* **15**: 6625-6641. The antisense nucleic acid molecule can also comprise a 2'-o-methylribonucleotide (*See, e.g.*, Inoue, *et al.* 1987. *Nucl. Acids Res.* **15**: 6131-6148) or a chimeric RNA-DNA analogue (*See, e.g.*, Inoue, *et al.*, 1987. *FEBS Lett.* **215**: 327-330).

Ribozymes and PNA Moieties

Nucleic acid modifications include, by way of non-limiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject.

In one embodiment, an antisense nucleic acid of the invention is a ribozyme. Ribozymes are catalytic RNA molecules with ribonuclease activity that are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (e.g., hammerhead ribozymes as described in Haselhoff and Gerlach 1988. *Nature* 334: 585-591) can be used to catalytically cleave NOVX mRNA transcripts to thereby inhibit translation of NOVX mRNA. A ribozyme having specificity for an NOVX-encoding nucleic acid can be designed based upon the nucleotide sequence of an NOVX cDNA disclosed herein (i.e., SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37). For example, a derivative of a *Tetrahymena* L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved in an NOVX-encoding mRNA. See, e.g., U.S. Patent 4,987,071 to Cech, *et al.* and U.S. Patent 5,116,742 to Cech, *et al.* NOVX mRNA can also be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules. See, e.g., Bartel *et al.*, (1993) *Science* 261:1411-1418.

Alternatively, NOVX gene expression can be inhibited by targeting nucleotide sequences complementary to the regulatory region of the NOVX nucleic acid (e.g., the NOVX promoter and/or enhancers) to form triple helical structures that prevent transcription of the NOVX gene in target cells. See, e.g., Helene, 1991. *Anticancer Drug Des.* 6: 569-84; Helene, *et al.* 1992. *Ann. N.Y. Acad. Sci.* 660: 27-36; Maher, 1992. *Bioassays* 14: 807-15.

In various embodiments, the NOVX nucleic acids can be modified at the base moiety, sugar moiety or phosphate backbone to improve, e.g., the stability, hybridization, or solubility of the molecule. For example, the deoxyribose phosphate backbone of the nucleic acids can be modified to generate peptide nucleic acids. See, e.g., Hyrup, *et al.*, 1996. *Bioorg Med Chem* 4: 5-23. As used herein, the terms "peptide nucleic acids" or "PNAs" refer to nucleic acid mimics

(e.g., DNA mimics) in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of PNAs has been shown to allow for specific hybridization to DNA and RNA under conditions of low ionic strength. The synthesis of PNA oligomers can be performed using standard solid phase peptide
5 synthesis protocols as described in Hyrup, *et al.*, 1996. *supra*; Perry-O'Keefe, *et al.*, 1996. *Proc. Natl. Acad. Sci. USA* 93: 14670-14675.

PNAs of NOVX can be used in therapeutic and diagnostic applications. For example, PNAs can be used as antisense or antigene agents for sequence-specific modulation of gene expression by, e.g., inducing transcription or translation arrest or inhibiting replication. PNAs of
10 NOVX can also be used, for example, in the analysis of single base pair mutations in a gene (e.g., PNA directed PCR clamping; as artificial restriction enzymes when used in combination with other enzymes, e.g., S₁ nucleases (See, Hyrup, *et al.*, 1996. *supra*); or as probes or primers for DNA sequence and hybridization (See, Hyrup, *et al.*, 1996, *supra*; Perry-O'Keefe, *et al.*, 1996. *supra*).

15 In another embodiment, PNAs of NOVX can be modified, e.g., to enhance their stability or cellular uptake, by attaching lipophilic or other helper groups to PNA, by the formation of PNA-DNA chimeras, or by the use of liposomes or other techniques of drug delivery known in the art. For example, PNA-DNA chimeras of NOVX can be generated that may combine the advantageous properties of PNA and DNA. Such chimeras allow DNA recognition enzymes
20 (e.g., RNase H and DNA polymerases) to interact with the DNA portion while the PNA portion would provide high binding affinity and specificity. PNA-DNA chimeras can be linked using linkers of appropriate lengths selected in terms of base stacking, number of bonds between the nucleobases, and orientation (see, Hyrup, *et al.*, 1996. *supra*). The synthesis of PNA-DNA chimeras can be performed as described in Hyrup, *et al.*, 1996. *supra* and Finn, *et al.*, 1996. *Nucl*
25 *Acids Res* 24: 3357-3363. For example, a DNA chain can be synthesized on a solid support using standard phosphoramidite coupling chemistry, and modified nucleoside analogs, e.g., 5'-(4-methoxytrityl)amino-5'-deoxy-thymidine phosphoramidite, can be used between the PNA and the 5' end of DNA. See, e.g., Mag, *et al.*, 1989. *Nucl Acid Res* 17: 5973-5988. PNA
30 monomers are then coupled in a stepwise manner to produce a chimeric molecule with a 5' PNA segment and a 3' DNA segment. See, e.g., Finn, *et al.*, 1996. *supra*. Alternatively, chimeric

molecules can be synthesized with a 5' DNA segment and a 3' PNA segment. *See, e.g., Petersen, et al., 1975. Bioorg. Med. Chem. Lett. 5: 1119-11124.*

In other embodiments, the oligonucleotide may include other appended groups such as peptides (*e.g., for targeting host cell receptors in vivo*), or agents facilitating transport across the cell membrane (*see, e.g., Letsinger, et al., 1989. Proc. Natl. Acad. Sci. U.S.A. 86: 6553-6556; Lemaitre, et al., 1987. Proc. Natl. Acad. Sci. 84: 648-652; PCT Publication No. WO88/09810*) or the blood-brain barrier (*see, e.g., PCT Publication No. WO 89/10134*). In addition, oligonucleotides can be modified with hybridization triggered cleavage agents (*see, e.g., Krol, et al., 1988. BioTechniques 6:958-976*) or intercalating agents (*see, e.g., Zon, 1988. Pharm. Res. 5: 539-549*). To this end, the oligonucleotide may be conjugated to another molecule, *e.g., a peptide, a hybridization triggered cross-linking agent, a transport agent, a hybridization-triggered cleavage agent, and the like.*

NOVX Polypeptides

A polypeptide according to the invention includes a polypeptide including the amino acid sequence of NOVX polypeptides whose sequences are provided in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, and 38. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residues shown in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, and 38 while still encoding a protein that maintains its NOVX activities and physiological functions, or a functional fragment thereof.

In general, an NOVX variant that preserves NOVX-like function includes any variant in which residues at a particular position in the sequence have been substituted by other amino acids, and further include the possibility of inserting an additional residue or residues between two residues of the parent protein as well as the possibility of deleting one or more residues from the parent sequence. Any amino acid substitution, insertion, or deletion is encompassed by the invention. In favorable circumstances, the substitution is a conservative substitution as defined above.

One aspect of the invention pertains to isolated NOVX proteins, and biologically-active portions thereof, or derivatives, fragments, analogs or homologs thereof. Also provided are polypeptide fragments suitable for use as immunogens to raise anti-NOVX antibodies. In one

embodiment, native NOVX proteins can be isolated from cells or tissue sources by an appropriate purification scheme using standard protein purification techniques. In another embodiment, NOVX proteins are produced by recombinant DNA techniques. Alternative to recombinant expression, an NOVX protein or polypeptide can be synthesized chemically using standard peptide synthesis techniques.

An "isolated" or "purified" polypeptide or protein or biologically-active portion thereof is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the NOVX protein is derived, or substantially free from chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of NOVX proteins in which the protein is separated from cellular components of the cells from which it is isolated or recombinantly-produced. In one embodiment, the language "substantially free of cellular material" includes preparations of NOVX proteins having less than about 30% (by dry weight) of non-NOVX proteins (also referred to herein as a "contaminating protein"), more preferably less than about 20% of non-NOVX proteins, still more preferably less than about 10% of non-NOVX proteins, and most preferably less than about 5% of non-NOVX proteins. When the NOVX protein or biologically-active portion thereof is recombinantly-produced, it is also preferably substantially free of culture medium, *i.e.*, culture medium represents less than about 20%, more preferably less than about 10%, and most preferably less than about 5% of the volume of the NOVX protein preparation.

The language "substantially free of chemical precursors or other chemicals" includes preparations of NOVX proteins in which the protein is separated from chemical precursors or other chemicals that are involved in the synthesis of the protein. In one embodiment, the language "substantially free of chemical precursors or other chemicals" includes preparations of NOVX proteins having less than about 30% (by dry weight) of chemical precursors or non-NOVX chemicals, more preferably less than about 20% chemical precursors or non-NOVX chemicals, still more preferably less than about 10% chemical precursors or non-NOVX chemicals, and most preferably less than about 5% chemical precursors or non-NOVX chemicals.

Biologically-active portions of NOVX proteins include peptides comprising amino acid sequences sufficiently homologous to or derived from the amino acid sequences of the NOVX proteins (*e.g.*, the amino acid sequence shown in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, and 38) that include fewer amino acids than the full-length NOVX

proteins, and exhibit at least one activity of an NOVX protein. Typically, biologically-active portions comprise a domain or motif with at least one activity of the NOVX protein. A biologically-active portion of an NOVX protein can be a polypeptide which is, for example, 10, 25, 50, 100 or more amino acid residues in length.

5 Moreover, other biologically-active portions, in which other regions of the protein are deleted, can be prepared by recombinant techniques and evaluated for one or more of the functional activities of a native NOVX protein.

In an embodiment, the NOVX protein has an amino acid sequence shown SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, and 38. In other embodiments, the NOVX protein is substantially homologous to SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, and 38, and retains the functional activity of the protein of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, and 38, yet differs in amino acid sequence due to natural allelic variation or mutagenesis, as described in detail, below.

10 Accordingly, in another embodiment, the NOVX protein is a protein that comprises an amino acid sequence at least about 45% homologous to the amino acid sequence SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, and 38, and retains the functional activity of the NOVX proteins of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, and 38.

20 **Determining Homology Between Two or More Sequences**

To determine the percent homology of two amino acid sequences or of two nucleic acids, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are homologous at that position (*i.e.*, as used herein amino acid or nucleic acid "homology" is equivalent to amino acid or nucleic acid "identity").

30 The nucleic acid sequence homology may be determined as the degree of identity between two sequences. The homology may be determined using computer programs known in the art, such as GAP software provided in the GCG program package. *See*, Needleman and Wunsch,

1970. *J Mol Biol* 48: 443-453. Using GCG GAP software with the following settings for nucleic acid sequence comparison: GAP creation penalty of 5.0 and GAP extension penalty of 0.3, the coding region of the analogous nucleic acid sequences referred to above exhibits a degree of identity preferably of at least 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99%, with the CDS
5 (encoding) part of the DNA sequence shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37. The term "sequence identity" refers to the degree to which two polynucleotide or polypeptide sequences are identical on a residue-by-residue basis over a particular region of comparison. The term "percentage of sequence identity" is calculated by comparing two optimally aligned sequences over that region of comparison, determining the
10 number of positions at which the identical nucleic acid base (*e.g.*, A, T, C, G, U, or I, in the case of nucleic acids) occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the region of comparison (*i.e.*, the window size), and multiplying the result by 100 to yield the percentage of sequence identity. The term "substantial identity" as used herein denotes a characteristic of a polynucleotide
15 sequence, wherein the polynucleotide comprises a sequence that has at least 80 percent sequence identity, preferably at least 85 percent identity and often 90 to 95 percent sequence identity, more usually at least 99 percent sequence identity as compared to a reference sequence over a comparison region.

20 **Chimeric and Fusion Proteins**

The invention also provides NOVX chimeric or fusion proteins. As used herein, an NOVX "chimeric protein" or "fusion protein" comprises an NOVX polypeptide operatively-linked to a non-NOVX polypeptide. An "NOVX polypeptide" refers to a polypeptide having an amino acid sequence corresponding to an NOVX protein SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16,
25 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, and 38, whereas a "non-NOVX polypeptide" refers to a polypeptide having an amino acid sequence corresponding to a protein that is not substantially homologous to the NOVX protein, *e.g.*, a protein that is different from the NOVX protein and that is derived from the same or a different organism. Within an NOVX fusion protein the NOVX polypeptide can correspond to all or a portion of an NOVX protein. In one embodiment, an
30 NOVX fusion protein comprises at least one biologically-active portion of an NOVX protein. In

another embodiment, an NOVX fusion protein comprises at least two biologically-active portions of an NOVX protein. In yet another embodiment, an NOVX fusion protein comprises at least three biologically-active portions of an NOVX protein. Within the fusion protein, the term "operatively-linked" is intended to indicate that the NOVX polypeptide and the non-NOVX polypeptide are fused in-frame with one another. The non-NOVX polypeptide can be fused to the N-terminus or C-terminus of the NOVX polypeptide.

In one embodiment, the fusion protein is a GST-NOVX fusion protein in which the NOVX sequences are fused to the C-terminus of the GST (glutathione S-transferase) sequences. Such fusion proteins can facilitate the purification of recombinant NOVX polypeptides.

In another embodiment, the fusion protein is an NOVX protein containing a heterologous signal sequence at its N-terminus. In certain host cells (*e.g.*, mammalian host cells), expression and/or secretion of NOVX can be increased through use of a heterologous signal sequence.

In yet another embodiment, the fusion protein is an NOVX-immunoglobulin fusion protein in which the NOVX sequences are fused to sequences derived from a member of the immunoglobulin protein family. The NOVX-immunoglobulin fusion proteins of the invention can be incorporated into pharmaceutical compositions and administered to a subject to inhibit an interaction between an NOVX ligand and an NOVX protein on the surface of a cell, to thereby suppress NOVX-mediated signal transduction *in vivo*. The NOVX-immunoglobulin fusion proteins can be used to affect the bioavailability of an NOVX cognate ligand. Inhibition of the NOVX ligand/NOVX interaction may be useful therapeutically for both the treatment of proliferative and differentiative disorders, as well as modulating (*e.g.* promoting or inhibiting) cell survival. Moreover, the NOVX-immunoglobulin fusion proteins of the invention can be used as immunogens to produce anti-NOVX antibodies in a subject, to purify NOVX ligands, and in screening assays to identify molecules that inhibit the interaction of NOVX with an NOVX ligand.

An NOVX chimeric or fusion protein of the invention can be produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different polypeptide sequences are ligated together in-frame in accordance with conventional techniques, *e.g.*, by employing blunt-ended or stagger-ended termini for ligation, restriction enzyme digestion to provide for appropriate termini, filling-in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and enzymatic ligation. In another embodiment, the fusion

gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers that give rise to complementary overhangs between two consecutive gene fragments that can subsequently be annealed and reamplified to generate a chimeric gene sequence (*see, e.g.,* 5 Ausubel, *et al.* (eds.) CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, 1992). Moreover, many expression vectors are commercially available that already encode a fusion moiety (*e.g.,* a GST polypeptide). An NOVX-encoding nucleic acid can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the NOVX protein.

10 NOVX Agonists and Antagonists

The invention also pertains to variants of the NOVX proteins that function as either NOVX agonists (*i.e.,* mimetics) or as NOVX antagonists. Variants of the NOVX protein can be generated by mutagenesis (*e.g.,* discrete point mutation or truncation of the NOVX protein). An agonist of the NOVX protein can retain substantially the same, or a subset of, the biological 15 activities of the naturally occurring form of the NOVX protein. An antagonist of the NOVX protein can inhibit one or more of the activities of the naturally occurring form of the NOVX protein by, for example, competitively binding to a downstream or upstream member of a cellular signaling cascade which includes the NOVX protein. Thus, specific biological effects can be elicited by treatment with a variant of limited function. In one embodiment, treatment of a subject 20 with a variant having a subset of the biological activities of the naturally occurring form of the protein has fewer side effects in a subject relative to treatment with the naturally occurring form of the NOVX proteins.

Variants of the NOVX proteins that function as either NOVX agonists (*i.e.,* mimetics) or as NOVX antagonists can be identified by screening combinatorial libraries of mutants (*e.g.,* 25 truncation mutants) of the NOVX proteins for NOVX protein agonist or antagonist activity. In one embodiment, a variegated library of NOVX variants is generated by combinatorial mutagenesis at the nucleic acid level and is encoded by a variegated gene library. A variegated library of NOVX variants can be produced by, for example, enzymatically ligating a mixture of synthetic oligonucleotides into gene sequences such that a degenerate set of potential NOVX 30 sequences is expressible as individual polypeptides, or alternatively, as a set of larger fusion

proteins (e.g., for phage display) containing the set of NOVX sequences therein. There are a variety of methods which can be used to produce libraries of potential NOVX variants from a degenerate oligonucleotide sequence. Chemical synthesis of a degenerate gene sequence can be performed in an automatic DNA synthesizer, and the synthetic gene then ligated into an appropriate expression vector. Use of a degenerate set of genes allows for the provision, in one mixture, of all of the sequences encoding the desired set of potential NOVX sequences. Methods for synthesizing degenerate oligonucleotides are well-known within the art. See, e.g., Narang, 1983. *Tetrahedron* 39: 3; Itakura, et al., 1984. *Annu. Rev. Biochem.* 53: 323; Itakura, et al., 1984. *Science* 198: 1056; Ike, et al., 1983. *Nucl. Acids Res.* 11: 477.

Polypeptide Libraries

In addition, libraries of fragments of the NOVX protein coding sequences can be used to generate a variegated population of NOVX fragments for screening and subsequent selection of variants of an NOVX protein. In one embodiment, a library of coding sequence fragments can be generated by treating a double stranded PCR fragment of an NOVX coding sequence with a nuclease under conditions wherein nicking occurs only about once per molecule, denaturing the double stranded DNA, renaturing the DNA to form double-stranded DNA that can include sense/antisense pairs from different nicked products, removing single stranded portions from reformed duplexes by treatment with S_1 nuclease, and ligating the resulting fragment library into an expression vector. By this method, expression libraries can be derived which encodes N-terminal and internal fragments of various sizes of the NOVX proteins.

Various techniques are known in the art for screening gene products of combinatorial libraries made by point mutations or truncation, and for screening cDNA libraries for gene products having a selected property. Such techniques are adaptable for rapid screening of the gene libraries generated by the combinatorial mutagenesis of NOVX proteins. The most widely used techniques, which are amenable to high throughput analysis, for screening large gene libraries typically include cloning the gene library into replicable expression vectors, transforming appropriate cells with the resulting library of vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates isolation of the vector encoding the gene whose product was detected. Recursive ensemble mutagenesis (REM), a new

technique that enhances the frequency of functional mutants in the libraries, can be used in combination with the screening assays to identify NOVX variants. *See, e.g., Arkin and Yourvan, 1992. Proc. Natl. Acad. Sci. USA 89: 7811-7815; Delgrave, et al., 1993. Protein Engineering 6:327-331.*

5

Anti-NOVX Antibodies

Also included in the invention are antibodies to NOVX proteins, or fragments of NOVX proteins. The term "antibody" as used herein refers to immunoglobulin molecules and immunologically active portions of immunoglobulin (Ig) molecules, i.e., molecules that contain
10 an antigen binding site that specifically binds (immunoreacts with) an antigen. Such antibodies include, but are not limited to, polyclonal, monoclonal, chimeric, single chain, F_{ab} , F_{ab}' and $F_{(ab)2}$ fragments, and an F_{ab} expression library. In general, an antibody molecule obtained from humans relates to any of the classes IgG, IgM, IgA, IgE and IgD, which differ from one another by the nature of the heavy chain present in the molecule. Certain classes have subclasses as well, such as
15 IgG₁, IgG₂, and others. Furthermore, in humans, the light chain may be a kappa chain or a lambda chain. Reference herein to antibodies includes a reference to all such classes, subclasses and types of human antibody species.

An isolated NOVX-related protein of the invention may be intended to serve as an antigen, or a portion or fragment thereof, and additionally can be used as an immunogen to generate
20 antibodies that immunospecifically bind the antigen, using standard techniques for polyclonal and monoclonal antibody preparation. The full-length protein can be used or, alternatively, the invention provides antigenic peptide fragments of the antigen for use as immunogens. An antigenic peptide fragment comprises at least 6 amino acid residues of the amino acid sequence of the full length protein and encompasses an epitope thereof such that an antibody raised against the
25 peptide forms a specific immune complex with the full length protein or with any fragment that contains the epitope. Preferably, the antigenic peptide comprises at least 10 amino acid residues, or at least 15 amino acid residues, or at least 20 amino acid residues, or at least 30 amino acid residues. Preferred epitopes encompassed by the antigenic peptide are regions of the protein that are located on its surface; commonly these are hydrophilic regions.

30 In certain embodiments of the invention, at least one epitope encompassed by the antigenic peptide is a region of NOVX-related protein that is located on the surface of the protein,

e.g., a hydrophilic region. A hydrophobicity analysis of the human NOVX-related protein sequence will indicate which regions of a NOVX-related protein are particularly hydrophilic and, therefore, are likely to encode surface residues useful for targeting antibody production. As a means for targeting antibody production, hydropathy plots showing regions of hydrophilicity and hydrophobicity may be generated by any method well known in the art, including, for example, the Kyte Doolittle or the Hopp Woods methods, either with or without Fourier transformation. See, e.g., Hopp and Woods, 1981, *Proc. Nat. Acad. Sci. USA* 78: 3824-3828; Kyte and Doolittle 1982, *J. Mol. Biol.* 157: 105-142, each of which is incorporated herein by reference in its entirety. Antibodies that are specific for one or more domains within an antigenic protein, or derivatives, fragments, analogs or homologs thereof, are also provided herein.

A protein of the invention, or a derivative, fragment, analog, homolog or ortholog thereof, may be utilized as an immunogen in the generation of antibodies that immunospecifically bind these protein components.

Various procedures known within the art may be used for the production of polyclonal or monoclonal antibodies directed against a protein of the invention, or against derivatives, fragments, analogs homologs or orthologs thereof (see, for example, *Antibodies: A Laboratory Manual*, Harlow and Lane, 1988, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, incorporated herein by reference). Some of these antibodies are discussed below.

Polyclonal Antibodies

For the production of polyclonal antibodies, various suitable host animals (e.g., rabbit, goat, mouse or other mammal) may be immunized by one or more injections with the native protein, a synthetic variant thereof, or a derivative of the foregoing. An appropriate immunogenic preparation can contain, for example, the naturally occurring immunogenic protein, a chemically synthesized polypeptide representing the immunogenic protein, or a recombinantly expressed immunogenic protein. Furthermore, the protein may be conjugated to a second protein known to be immunogenic in the mammal being immunized. Examples of such immunogenic proteins include but are not limited to keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, and soybean trypsin inhibitor. The preparation can further include an adjuvant. Various adjuvants used to increase the immunological response include, but are not limited to, Freund's (complete and incomplete), mineral gels (e.g., aluminum hydroxide), surface active substances (e.g., lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, dinitrophenol, etc.), adjuvants

usable in humans such as Bacille Calmette-Guerin and Corynebacterium parvum, or similar immunostimulatory agents. Additional examples of adjuvants which can be employed include MPL-TDM adjuvant (monophosphoryl Lipid A, synthetic trehalose dicorynomycolate).

5 The polyclonal antibody molecules directed against the immunogenic protein can be isolated from the mammal (e.g., from the blood) and further purified by well known techniques, such as affinity chromatography using protein A or protein G, which provide primarily the IgG fraction of immune serum. Subsequently, or alternatively, the specific antigen which is the target of the immunoglobulin sought, or an epitope thereof, may be immobilized on a column to purify the immune specific antibody by immunoaffinity chromatography. Purification of
10 immunoglobulins is discussed, for example, by D. Wilkinson (The Scientist, published by The Scientist, Inc., Philadelphia PA, Vol. 14, No. 8 (April 17, 2000), pp. 25-28).

Monoclonal Antibodies

The term "monoclonal antibody" (MAb) or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one molecular species of
15 antibody molecule consisting of a unique light chain gene product and a unique heavy chain gene product. In particular, the complementarity determining regions (CDRs) of the monoclonal antibody are identical in all the molecules of the population. MAbs thus contain an antigen binding site capable of immunoreacting with a particular epitope of the antigen characterized by a unique binding affinity for it.

20 Monoclonal antibodies can be prepared using hybridoma methods, such as those described by Kohler and Milstein, *Nature*, 256:495 (1975). In a hybridoma method, a mouse, hamster, or other appropriate host animal, is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes can be immunized in vitro.

25 The immunizing agent will typically include the protein antigen, a fragment thereof or a fusion protein thereof. Generally, either peripheral blood lymphocytes are used if cells of human origin are desired, or spleen cells or lymph node cells are used if non-human mammalian sources are desired. The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, MONOCLONAL
30 ANTIBODIES: PRINCIPLES AND PRACTICE, Academic Press, (1986) pp. 59-103). Immortalized cell lines are usually transformed mammalian cells, particularly myeloma cells of rodent, bovine and

human origin. Usually, rat or mouse myeloma cell lines are employed. The hybridoma cells can be cultured in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, immortalized cells. For example, if the parental cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine ("HAT medium"), which substances prevent the growth of HGPRT-deficient cells.

Preferred immortalized cell lines are those that fuse efficiently, support stable high level expression of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. More preferred immortalized cell lines are murine myeloma lines, which can be obtained, for instance, from the Salk Institute Cell Distribution Center, San Diego, California and the American Type Culture Collection, Manassas, Virginia. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies (Kozbor, *J. Immunol.*, 133:3001 (1984); Brodeur et al., *MONOCLONAL ANTIBODY PRODUCTION TECHNIQUES AND APPLICATIONS*, Marcel Dekker, Inc., New York, (1987) pp. 51-63).

The culture medium in which the hybridoma cells are cultured can then be assayed for the presence of monoclonal antibodies directed against the antigen. Preferably, the binding specificity of monoclonal antibodies produced by the hybridoma cells is determined by immunoprecipitation or by an in vitro binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA). Such techniques and assays are known in the art. The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson and Pollard, *Anal. Biochem.*, 107:220 (1980). Preferably, antibodies having a high degree of specificity and a high binding affinity for the target antigen are isolated.

After the desired hybridoma cells are identified, the clones can be subcloned by limiting dilution procedures and grown by standard methods. Suitable culture media for this purpose include, for example, Dulbecco's Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the hybridoma cells can be grown in vivo as ascites in a mammal.

The monoclonal antibodies secreted by the subclones can be isolated or purified from the culture medium or ascites fluid by conventional immunoglobulin purification procedures such as,

for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

The monoclonal antibodies can also be made by recombinant DNA methods, such as those described in U.S. Patent No. 4,816,567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells of the invention serve as a preferred source of such DNA. Once isolated, the DNA can be placed into expression vectors, which are then transfected into host cells such as simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also can be modified, for example, by substituting the coding sequence for human heavy and light chain constant domains in place of the homologous murine sequences (U.S. Patent No. 4,816,567; Morrison, *Nature* 368, 812-13 (1994)) or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the constant domains of an antibody of the invention, or can be substituted for the variable domains of one antigen-combining site of an antibody of the invention to create a chimeric bivalent antibody.

Humanized Antibodies

The antibodies directed against the protein antigens of the invention can further comprise humanized antibodies or human antibodies. These antibodies are suitable for administration to humans without engendering an immune response by the human against the administered immunoglobulin. Humanized forms of antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')₂ or other antigen-binding subsequences of antibodies) that are principally comprised of the sequence of a human immunoglobulin, and contain minimal sequence derived from a non-human immunoglobulin. Humanization can be performed following the method of Winter and co-workers (Jones et al., *Nature*, 321:522-525 (1986); Riechmann et al., *Nature*, 332:323-327 (1988); Verhoeyen et al., *Science*, 239:1534-1536 (1988)), by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. (See also U.S. Patent No. 5,225,539.) In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding

non-human residues. Humanized antibodies can also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the framework regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin (Jones et al., 1986; Riechmann et al., 1988; and Presta, *Curr. Op. Struct. Biol.*, 2:593-596 (1992)).

Human Antibodies

Fully human antibodies relate to antibody molecules in which essentially the entire sequences of both the light chain and the heavy chain, including the CDRs, arise from human genes. Such antibodies are termed "human antibodies", or "fully human antibodies" herein. Human monoclonal antibodies can be prepared by the trioma technique; the human B-cell hybridoma technique (see Kozbor, et al., 1983 *Immunol Today* 4: 72) and the EBV hybridoma technique to produce human monoclonal antibodies (see Cole, et al., 1985 In: *MONOCLONAL ANTIBODIES AND CANCER THERAPY*, Alan R. Liss, Inc., pp. 77-96). Human monoclonal antibodies may be utilized in the practice of the present invention and may be produced by using human hybridomas (see Cote, et al., 1983. *Proc Natl Acad Sci USA* 80: 2026-2030) or by transforming human B-cells with Epstein Barr Virus in vitro (see Cole, et al., 1985 In: *MONOCLONAL ANTIBODIES AND CANCER THERAPY*, Alan R. Liss, Inc., pp. 77-96).

In addition, human antibodies can also be produced using additional techniques, including phage display libraries (Hoogenboom and Winter, *J. Mol. Biol.*, 227:381 (1991); Marks et al., *J. Mol. Biol.*, 222:581 (1991)). Similarly, human antibodies can be made by introducing human immunoglobulin loci into transgenic animals, e.g., mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. Upon challenge, human antibody production is observed, which closely resembles that seen in humans in all respects, including gene rearrangement, assembly, and antibody repertoire. This approach is described, for example, in U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,661,016, and in Marks et al. (*Bio/Technology* 10, 779-783 (1992)); Lonberg et al. (*Nature* 368 856-859 (1994)); Morrison (*Nature* 368, 812-13 (1994)); Fishwild et al. (*Nature Biotechnology* 14, 845-

51 (1996)); Neuberger (*Nature Biotechnology* 14, 826 (1996)); and Lonberg and Huszar (*Intern. Rev. Immunol.* 13 65-93 (1995)).

Human antibodies may additionally be produced using transgenic nonhuman animals which are modified so as to produce fully human antibodies rather than the animal's endogenous antibodies in response to challenge by an antigen. (See PCT publication WO94/02602). The endogenous genes encoding the heavy and light immunoglobulin chains in the nonhuman host have been incapacitated, and active loci encoding human heavy and light chain immunoglobulins are inserted into the host's genome. The human genes are incorporated, for example, using yeast artificial chromosomes containing the requisite human DNA segments. An animal which provides all the desired modifications is then obtained as progeny by crossbreeding intermediate transgenic animals containing fewer than the full complement of the modifications. The preferred embodiment of such a nonhuman animal is a mouse, and is termed the XenomouseTM as disclosed in PCT publications WO 96/33735 and WO 96/34096. This animal produces B cells which secrete fully human immunoglobulins. The antibodies can be obtained directly from the animal after immunization with an immunogen of interest, as, for example, a preparation of a polyclonal antibody, or alternatively from immortalized B cells derived from the animal, such as hybridomas producing monoclonal antibodies. Additionally, the genes encoding the immunoglobulins with human variable regions can be recovered and expressed to obtain the antibodies directly, or can be further modified to obtain analogs of antibodies such as, for example, single chain Fv molecules.

An example of a method of producing a nonhuman host, exemplified as a mouse, lacking expression of an endogenous immunoglobulin heavy chain is disclosed in U.S. Patent No. 5,939,598. It can be obtained by a method including deleting the J segment genes from at least one endogenous heavy chain locus in an embryonic stem cell to prevent rearrangement of the locus and to prevent formation of a transcript of a rearranged immunoglobulin heavy chain locus, the deletion being effected by a targeting vector containing a gene encoding a selectable marker; and producing from the embryonic stem cell a transgenic mouse whose somatic and germ cells contain the gene encoding the selectable marker.

A method for producing an antibody of interest, such as a human antibody, is disclosed in U.S. Patent No. 5,916,771. It includes introducing an expression vector that contains a nucleotide sequence encoding a heavy chain into one mammalian host cell in culture, introducing an expression vector containing a nucleotide sequence encoding a light chain into another

mammalian host cell, and fusing the two cells to form a hybrid cell. The hybrid cell expresses an antibody containing the heavy chain and the light chain.

In a further improvement on this procedure, a method for identifying a clinically relevant epitope on an immunogen, and a correlative method for selecting an antibody that binds immunospecifically to the relevant epitope with high affinity, are disclosed in PCT publication WO 99/53049.

F_{ab} Fragments and Single Chain Antibodies

According to the invention, techniques can be adapted for the production of single-chain antibodies specific to an antigenic protein of the invention (see e.g., U.S. Patent No. 4,946,778).

10 In addition, methods can be adapted for the construction of F_{ab} expression libraries (see e.g., Huse, et al., 1989 Science 246: 1275-1281) to allow rapid and effective identification of monoclonal F_{ab} fragments with the desired specificity for a protein or derivatives, fragments, analogs or homologs thereof. Antibody fragments that contain the idiotypes to a protein antigen may be produced by techniques known in the art including, but not limited to: (i) an F_{(ab')₂} fragment produced by
15 pepsin digestion of an antibody molecule; (ii) an F_{ab} fragment generated by reducing the disulfide bridges of an F_{(ab')₂} fragment; (iii) an F_{ab} fragment generated by the treatment of the antibody molecule with papain and a reducing agent and (iv) F_v fragments.

Bispecific Antibodies

Bispecific antibodies are monoclonal, preferably human or humanized, antibodies that
20 have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for an antigenic protein of the invention. The second binding target is any other antigen, and advantageously is a cell-surface protein or receptor or receptor subunit.

Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two
25 immunoglobulin heavy-chain/light-chain pairs, where the two heavy chains have different specificities (Milstein and Cuello, *Nature*, 305:537-539 (1983)). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of ten different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule is usually accomplished by affinity

chromatography steps. Similar procedures are disclosed in WO 93/08829, published 13 May 1993, and in Traunecker *et al.*, 1991 *EMBO J.*, 10:3655-3659.

Antibody variable domains with the desired binding specificities (antibody-antigen combining sites) can be fused to immunoglobulin constant domain sequences. The fusion preferably is with an immunoglobulin heavy-chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. It is preferred to have the first heavy-chain constant region (CH1) containing the site necessary for light-chain binding present in at least one of the fusions. DNAs encoding the immunoglobulin heavy-chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host organism. For further details of generating bispecific antibodies see, for example, Suresh *et al.*, *Methods in Enzymology*, 121:210 (1986).

According to another approach described in WO 96/27011, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered from recombinant cell culture. The preferred interface comprises at least a part of the CH3 region of an antibody constant domain. In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (e.g. tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the large side chain(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (e.g. alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

Bispecific antibodies can be prepared as full length antibodies or antibody fragments (e.g. F(ab')₂ bispecific antibodies). Techniques for generating bispecific antibodies from antibody fragments have been described in the literature. For example, bispecific antibodies can be prepared using chemical linkage. Brennan *et al.*, *Science* 229:81 (1985) describe a procedure wherein intact antibodies are proteolytically cleaved to generate F(ab')₂ fragments. These fragments are reduced in the presence of the dithiol complexing agent sodium arsenite to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-thiol by reduction with mercaptoethylamine and is mixed with an equimolar amount of the other Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

Additionally, Fab' fragments can be directly recovered from *E. coli* and chemically coupled to form bispecific antibodies. Shalaby et al., *J. Exp. Med.* 175:217-225 (1992) describe the production of a fully humanized bispecific antibody F(ab')₂ molecule. Each Fab' fragment was separately secreted from *E. coli* and subjected to directed chemical coupling in vitro to form the bispecific antibody. The bispecific antibody thus formed was able to bind to cells overexpressing the ErbB2 receptor and normal human T cells, as well as trigger the lytic activity of human cytotoxic lymphocytes against human breast tumor targets.

Various techniques for making and isolating bispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers. Kostelny et al., *J. Immunol.* 148(5):1547-1553 (1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers were reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. This method can also be utilized for the production of antibody homodimers. The "diabody" technology described by Hollinger et al., *Proc. Natl. Acad. Sci. USA* 90:6444-6448 (1993) has provided an alternative mechanism for making bispecific antibody fragments. The fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the V_H and V_L domains of one fragment are forced to pair with the complementary V_L and V_H domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. See, Gruber et al., *J. Immunol.* 152:5368 (1994).

Antibodies with more than two valencies are contemplated. For example, trispecific antibodies can be prepared. Tutt et al., *J. Immunol.* 147:60 (1991).

Exemplary bispecific antibodies can bind to two different epitopes, at least one of which originates in the protein antigen of the invention. Alternatively, an anti-antigenic arm of an immunoglobulin molecule can be combined with an arm which binds to a triggering molecule on a leukocyte such as a T-cell receptor molecule (e.g. CD2, CD3, CD28, or B7), or Fc receptors for IgG (FcγR), such as FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16) so as to focus cellular defense mechanisms to the cell expressing the particular antigen. Bispecific antibodies can also be used to direct cytotoxic agents to cells which express a particular antigen. These antibodies

possess an antigen-binding arm and an arm which binds a cytotoxic agent or a radionuclide chelator, such as EOTUBE, DPTA, DOTA, or TETA. Another bispecific antibody of interest binds the protein antigen described herein and further binds tissue factor (TF).

Heteroconjugate Antibodies

5 Heteroconjugate antibodies are also within the scope of the present invention.

Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells (U.S. Patent No. 4,676,980), and for treatment of HIV infection (WO 91/00360; WO 92/200373; EP 03089). It is contemplated that the antibodies can be prepared in vitro using known methods in synthetic
10 protein chemistry, including those involving crosslinking agents. For example, immunotoxins can be constructed using a disulfide exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptobutyrimidate and those disclosed, for example, in U.S. Patent No. 4,676,980.

Effector Function Engineering

15 It can be desirable to modify the antibody of the invention with respect to effector function, so as to enhance, e.g., the effectiveness of the antibody in treating cancer. For example, cysteine residue(s) can be introduced into the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated can have improved internalization capability and/or increased complement-mediated cell killing and antibody-
20 dependent cellular cytotoxicity (ADCC). See Caron et al., J. Exp Med., 176: 1191-1195 (1992) and Shopes, J. Immunol., 148: 2918-2922 (1992). Homodimeric antibodies with enhanced anti-tumor activity can also be prepared using heterobifunctional cross-linkers as described in Wolff et al. Cancer Research, 53: 2560-2565 (1993). Alternatively, an antibody can be engineered that has dual Fc regions and can thereby have enhanced complement lysis and ADCC capabilities. See
25 Stevenson et al., Anti-Cancer Drug Design, 3: 219-230 (1989).

Immunoconjugates

The invention also pertains to immunoconjugates comprising an antibody conjugated to a cytotoxic agent such as a chemotherapeutic agent, toxin (e.g., an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (i.e., a
30 radioconjugate).

Chemotherapeutic agents useful in the generation of such immunoconjugates have been described above. Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, Aleurites
5 *fordii* proteins, dianthin proteins, *Phytolaca americana* proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes. A variety of radionuclides are available for the production of radioconjugated antibodies. Examples include ^{212}Bi , ^{131}I , ^{131}In , ^{90}Y , and ^{186}Re .

10 Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido
15 compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta et al., Science, 238: 1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See
20 WO94/11026.

In another embodiment, the antibody can be conjugated to a "receptor" (such streptavidin) for utilization in tumor pretargeting wherein the antibody-receptor conjugate is administered to the patient, followed by removal of unbound conjugate from the circulation using a clearing agent and then administration of a "ligand" (e.g., avidin) that is in turn conjugated to a cytotoxic agent.

25 In one embodiment, methods for the screening of antibodies that possess the desired specificity include, but are not limited to, enzyme-linked immunosorbent assay (ELISA) and other immunologically-mediated techniques known within the art. In a specific embodiment, selection of antibodies that are specific to a particular domain of an NOVX protein is facilitated by generation of hybridomas that bind to the fragment of an NOVX protein possessing such a
30 domain. Thus, antibodies that are specific for a desired domain within an NOVX protein, or derivatives, fragments, analogs or homologs thereof, are also provided herein.

Anti-NOVX antibodies may be used in methods known within the art relating to the localization and/or quantitation of an NOVX protein (*e.g.*, for use in measuring levels of the NOVX protein within appropriate physiological samples, for use in diagnostic methods, for use in imaging the protein, and the like). In a given embodiment, antibodies for NOVX proteins, or derivatives, fragments, analogs or homologs thereof, that contain the antibody derived binding domain, are utilized as pharmacologically-active compounds (hereinafter "Therapeutics").

An anti-NOVX antibody (*e.g.*, monoclonal antibody) can be used to isolate an NOVX polypeptide by standard techniques, such as affinity chromatography or immunoprecipitation. An anti-NOVX antibody can facilitate the purification of natural NOVX polypeptide from cells and of recombinantly-produced NOVX polypeptide expressed in host cells. Moreover, an anti-NOVX antibody can be used to detect NOVX protein (*e.g.*, in a cellular lysate or cell supernatant) in order to evaluate the abundance and pattern of expression of the NOVX protein. Anti-NOVX antibodies can be used diagnostically to monitor protein levels in tissue as part of a clinical testing procedure, *e.g.*, to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling (*i.e.*, physically linking) the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β -galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I , ^{131}I , ^{35}S or ^3H .

NOVX Recombinant Expression Vectors and Host Cells

Another aspect of the invention pertains to vectors, preferably expression vectors, containing a nucleic acid encoding an NOVX protein, or derivatives, fragments, analogs or homologs thereof. As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments can be

ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively-linked. Such vectors are referred to herein as "expression vectors". In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" can be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

The recombinant expression vectors of the invention comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell, which means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, that is operatively-linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably-linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner that allows for expression of the nucleotide sequence (*e.g.*, in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell).

The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel, GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990). Regulatory sequences include those that direct constitutive expression of a nucleotide sequence in many types of host cell and those that direct expression of the nucleotide sequence only in certain host cells (*e.g.*, tissue-specific regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, etc. The expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded

by nucleic acids as described herein (e.g., NOVX proteins, mutant forms of NOVX proteins, fusion proteins, etc.).

The recombinant expression vectors of the invention can be designed for expression of NOVX proteins in prokaryotic or eukaryotic cells. For example, NOVX proteins can be expressed in bacterial cells such as *Escherichia coli*, insect cells (using baculovirus expression vectors) yeast cells or mammalian cells. Suitable host cells are discussed further in Goeddel, GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990). Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example using T7 promoter regulatory sequences and T7 polymerase.

Expression of proteins in prokaryotes is most often carried out in *Escherichia coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a protein encoded therein, usually to the amino terminus of the recombinant protein. Such fusion vectors typically serve three purposes: (i) to increase expression of recombinant protein; (ii) to increase the solubility of the recombinant protein; and (iii) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification. Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase. Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith and Johnson, 1988. *Gene* 67: 31-40), pMAL (New England Biolabs, Beverly, Mass.) and pRIT5 (Pharmacia, Piscataway, N.J.) that fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein.

Examples of suitable inducible non-fusion *E. coli* expression vectors include pTrc (Amrann *et al.*, (1988) *Gene* 69:301-315) and pET 11d (Studier *et al.*, GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990) 60-89).

One strategy to maximize recombinant protein expression in *E. coli* is to express the protein in a host bacteria with an impaired capacity to proteolytically cleave the recombinant protein. See, e.g., Gottesman, GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990) 119-128. Another strategy is to alter the nucleic acid sequence of the nucleic acid to be inserted into an expression vector so that the individual codons

for each amino acid are those preferentially utilized in *E. coli* (see, e.g., Wada, *et al.*, 1992. *Nucl. Acids Res.* 20: 2111-2118). Such alteration of nucleic acid sequences of the invention can be carried out by standard DNA synthesis techniques.

In another embodiment, the NOVX expression vector is a yeast expression vector.

- 5 Examples of vectors for expression in yeast *Saccharomyces cerevisiae* include pYepSec1 (Baldari, *et al.*, 1987. *EMBO J.* 6: 229-234), pMFa (Kurjan and Herskowitz, 1982. *Cell* 30: 933-943), pJRY88 (Schultz *et al.*, 1987. *Gene* 54: 113-123), pYES2 (Invitrogen Corporation, San Diego, Calif.), and picZ (Invitrogen Corp, San Diego, Calif.).

- 10 Alternatively, NOVX can be expressed in insect cells using baculovirus expression vectors. Baculovirus vectors available for expression of proteins in cultured insect cells (e.g., SF9 cells) include the pAc series (Smith, *et al.*, 1983. *Mol. Cell. Biol.* 3: 2156-2165) and the pVL series (Lucklow and Summers, 1989. *Virology* 170: 31-39).

- 15 In yet another embodiment, a nucleic acid of the invention is expressed in mammalian cells using a mammalian expression vector. Examples of mammalian expression vectors include pCDM8 (Seed, 1987. *Nature* 329: 840) and pMT2PC (Kaufman, *et al.*, 1987. *EMBO J.* 6: 187-195). When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. For example, commonly used promoters are derived from polyoma, adenovirus 2, cytomegalovirus, and simian virus 40. For other suitable expression systems for both prokaryotic and eukaryotic cells see, e.g., Chapters 16 and 17 of Sambrook, *et al.*, MOLECULAR CLONING: A LABORATORY MANUAL. 2nd ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989.

- 20 In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid preferentially in a particular cell type (e.g., tissue-specific regulatory elements are used to express the nucleic acid). Tissue-specific regulatory elements are known in the art. Non-limiting examples of suitable tissue-specific promoters include the albumin promoter (liver-specific; Pinkert, *et al.*, 1987. *Genes Dev.* 1: 268-277), lymphoid-specific promoters (Calame and Eaton, 1988. *Adv. Immunol.* 43: 235-275), in particular promoters of T cell receptors (Winoto and Baltimore, 1989. *EMBO J.* 8: 729-733) and immunoglobulins (Banerji, *et al.*, 1983. *Cell* 33: 729-740; Queen and Baltimore, 1983. *Cell* 33: 741-748), neuron-specific promoters (e.g., the neurofilament promoter; Byrne and Ruddle, 1989. *Proc. Natl. Acad. Sci. USA* 86: 5473-5477), pancreas-specific promoters (Edlund, *et al.*, 1985. *Science* 230: 912-916), and

mammary gland-specific promoters (*e.g.*, milk whey promoter; U.S. Pat. No. 4,873,316 and European Application Publication No. 264,166). Developmentally-regulated promoters are also encompassed, *e.g.*, the murine hox promoters (Kessel and Gruss, 1990. *Science* 249: 374-379) and the α -fetoprotein promoter (Campes and Tilghman, 1989. *Genes Dev.* 3: 537-546).

5 The invention further provides a recombinant expression vector comprising a DNA molecule of the invention cloned into the expression vector in an antisense orientation. That is, the DNA molecule is operatively-linked to a regulatory sequence in a manner that allows for expression (by transcription of the DNA molecule) of an RNA molecule that is antisense to NOVX mRNA. Regulatory sequences operatively linked to a nucleic acid cloned in the antisense
10 orientation can be chosen that direct the continuous expression of the antisense RNA molecule in a variety of cell types, for instance viral promoters and/or enhancers, or regulatory sequences can be chosen that direct constitutive, tissue specific or cell type specific expression of antisense RNA. The antisense expression vector can be in the form of a recombinant plasmid, phagemid or attenuated virus in which antisense nucleic acids are produced under the control of a high
15 efficiency regulatory region, the activity of which can be determined by the cell type into which the vector is introduced. For a discussion of the regulation of gene expression using antisense genes *see, e.g.*, Weintraub, *et al.*, "Antisense RNA as a molecular tool for genetic analysis," *Reviews-Trends in Genetics*, Vol. 1(1) 1986.

20 Another aspect of the invention pertains to host cells into which a recombinant expression vector of the invention has been introduced. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but also to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included
25 within the scope of the term as used herein.

A host cell can be any prokaryotic or eukaryotic cell. For example, NOVX protein can be expressed in bacterial cells such as *E. coli*, insect cells, yeast or mammalian cells (such as Chinese hamster ovary cells (CHO) or COS cells). Other suitable host cells are known to those skilled in the art.

30 Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and

"transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid (*e.g.*, DNA) into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook, *et al.* (MOLECULAR CLONING: A LABORATORY MANUAL. 2nd ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989), and other laboratory manuals.

For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene that encodes a selectable marker (*e.g.*, resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Various selectable markers include those that confer resistance to drugs, such as G418, hygromycin and methotrexate. Nucleic acid encoding a selectable marker can be introduced into a host cell on the same vector as that encoding NOVX or can be introduced on a separate vector. Cells stably transfected with the introduced nucleic acid can be identified by drug selection (*e.g.*, cells that have incorporated the selectable marker gene will survive, while the other cells die).

A host cell of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce (*i.e.*, express) NOVX protein. Accordingly, the invention further provides methods for producing NOVX protein using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of invention (into which a recombinant expression vector encoding NOVX protein has been introduced) in a suitable medium such that NOVX protein is produced. In another embodiment, the method further comprises isolating NOVX protein from the medium or the host cell.

25 Transgenic NOVX Animals

The host cells of the invention can also be used to produce non-human transgenic animals. For example, in one embodiment, a host cell of the invention is a fertilized oocyte or an embryonic stem cell into which NOVX protein-coding sequences have been introduced. Such host cells can then be used to create non-human transgenic animals in which exogenous NOVX sequences have been introduced into their genome or homologous recombinant animals in which

endogenous NOVX sequences have been altered. Such animals are useful for studying the function and/or activity of NOVX protein and for identifying and/or evaluating modulators of NOVX protein activity. As used herein, a "transgenic animal" is a non-human animal, preferably a mammal, more preferably a rodent such as a rat or mouse, in which one or more of the cells of the animal includes a transgene. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens, amphibians, etc. A transgene is exogenous DNA that is integrated into the genome of a cell from which a transgenic animal develops and that remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, a "homologous recombinant animal" is a non-human animal, preferably a mammal, more preferably a mouse, in which an endogenous NOVX gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, e.g., an embryonic cell of the animal, prior to development of the animal.

A transgenic animal of the invention can be created by introducing NOVX-encoding nucleic acid into the male pronuclei of a fertilized oocyte (e.g., by microinjection, retroviral infection) and allowing the oocyte to develop in a pseudopregnant female foster animal. The human NOVX cDNA sequences SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37 can be introduced as a transgene into the genome of a non-human animal. Alternatively, a non-human homologue of the human NOVX gene, such as a mouse NOVX gene, can be isolated based on hybridization to the human NOVX cDNA (described further *supra*) and used as a transgene. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene. A tissue-specific regulatory sequence(s) can be operably-linked to the NOVX transgene to direct expression of NOVX protein to particular cells. Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866; 4,870,009; and 4,873,191; and Hogan, 1986. In: MANIPULATING THE MOUSE EMBRYO, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of the NOVX transgene in its genome and/or expression of NOVX mRNA in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover,

transgenic animals carrying a transgene-encoding NOVX protein can further be bred to other transgenic animals carrying other transgenes.

To create a homologous recombinant animal, a vector is prepared which contains at least a portion of an NOVX gene into which a deletion, addition or substitution has been introduced to thereby alter, *e.g.*, functionally disrupt, the NOVX gene. The NOVX gene can be a human gene (e.g., the cDNA of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37), but more preferably, is a non-human homologue of a human NOVX gene. For example, a mouse homologue of human NOVX gene of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37 can be used to construct a homologous recombination vector suitable for altering an endogenous NOVX gene in the mouse genome. In one embodiment, the vector is designed such that, upon homologous recombination, the endogenous NOVX gene is functionally disrupted (*i.e.*, no longer encodes a functional protein; also referred to as a "knock out" vector).

Alternatively, the vector can be designed such that, upon homologous recombination, the endogenous NOVX gene is mutated or otherwise altered but still encodes functional protein (e.g., the upstream regulatory region can be altered to thereby alter the expression of the endogenous NOVX protein). In the homologous recombination vector, the altered portion of the NOVX gene is flanked at its 5'- and 3'-termini by additional nucleic acid of the NOVX gene to allow for homologous recombination to occur between the exogenous NOVX gene carried by the vector and an endogenous NOVX gene in an embryonic stem cell. The additional flanking NOVX nucleic acid is of sufficient length for successful homologous recombination with the endogenous gene. Typically, several kilobases of flanking DNA (both at the 5'- and 3'-termini) are included in the vector. *See, e.g.*, Thomas, *et al.*, 1987. *Cell* 51: 503 for a description of homologous recombination vectors. The vector is then introduced into an embryonic stem cell line (e.g., by electroporation) and cells in which the introduced NOVX gene has homologously-recombined with the endogenous NOVX gene are selected. *See, e.g.*, Li, *et al.*, 1992. *Cell* 69: 915.

The selected cells are then injected into a blastocyst of an animal (e.g., a mouse) to form aggregation chimeras. *See, e.g.*, Bradley, 1987. In: TERATOCARCINOMAS AND EMBRYONIC STEM CELLS: A PRACTICAL APPROACH, Robertson, ed. IRL, Oxford, pp. 113-152. A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term. Progeny harboring the homologously-recombined DNA in their germ cells can

be used to breed animals in which all cells of the animal contain the homologously-recombined DNA by germline transmission of the transgene. Methods for constructing homologous recombination vectors and homologous recombinant animals are described further in Bradley, 1991. *Curr. Opin. Biotechnol.* 2: 823-829; PCT International Publication Nos.: WO 90/11354; 5 WO 91/01140; WO 92/0968; and WO 93/04169.

In another embodiment, transgenic non-humans animals can be produced that contain selected systems that allow for regulated expression of the transgene. One example of such a system is the cre/loxP recombinase system of bacteriophage P1. For a description of the cre/loxP recombinase system, See, e.g., Lakso, *et al.*, 1992. *Proc. Natl. Acad. Sci. USA* 89: 6232-6236.

10 Another example of a recombinase system is the FLP recombinase system of *Saccharomyces cerevisiae*. See, O'Gorman, *et al.*, 1991. *Science* 251:1351-1355. If a cre/loxP recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the Cre recombinase and a selected protein are required. Such animals can be provided through the construction of "double" transgenic animals, e.g., by mating two transgenic animals, 15 one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase.

Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut, *et al.*, 1997. *Nature* 385: 810-813. In brief, a cell (e.g., a somatic cell) from the transgenic animal can be isolated and induced to exit the growth 20 cycle and enter G₀ phase. The quiescent cell can then be fused, e.g., through the use of electrical pulses, to an enucleated oocyte from an animal of the same species from which the quiescent cell is isolated. The reconstructed oocyte is then cultured such that it develops to morula or blastocyte and then transferred to pseudopregnant female foster animal. The offspring borne of this female foster animal will be a clone of the animal from which the cell (e.g., the somatic cell) is isolated.

25 **Pharmaceutical Compositions**

The NOVX nucleic acid molecules, NOVX proteins, and anti-NOVX antibodies (also referred to herein as "active compounds") of the invention, and derivatives, fragments, analogs and homologs thereof, can be incorporated into pharmaceutical compositions suitable for 30 administration. Such compositions typically comprise the nucleic acid molecule, protein, or

antibody and a pharmaceutically acceptable carrier. As used herein, "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. Suitable carriers are described in the most recent edition of
5 Remington's Pharmaceutical Sciences, a standard reference text in the field, which is incorporated herein by reference. Preferred examples of such carriers or diluents include, but are not limited to, water, saline, finger's solutions, dextrose solution, and 5% human serum albumin. Liposomes and non-aqueous vehicles such as fixed oils may also be used. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any
10 conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*,
15 intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (*i.e.*, topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens;
20 antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

25 Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the
30 extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as

bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound (e.g., an NOVX protein or anti-NOVX antibody) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

Systemic administration can also be by transmucosal or transdermal means. For
5 transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into
10 ointments, salves, gels, or creams as generally known in the art.

The compounds can also be prepared in the form of suppositories (*e.g.*, with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

In one embodiment, the active compounds are prepared with carriers that will protect the
15 compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza
20 Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

It is especially advantageous to formulate oral or parenteral compositions in dosage unit
25 form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique
30 characteristics of the active compound and the particular therapeutic effect to be achieved, and the

limitations inherent in the art of compounding such an active compound for the treatment of individuals.

The nucleic acid molecules of the invention can be inserted into vectors and used as gene therapy vectors. Gene therapy vectors can be delivered to a subject by, for example, intravenous injection, local administration (*see, e.g.*, U.S. Patent No. 5,328,470) or by stereotactic injection (*see, e.g.*, Chen, *et al.*, 1994. *Proc. Natl. Acad. Sci. USA* 91: 3054-3057). The pharmaceutical preparation of the gene therapy vector can include the gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, *e.g.*, retroviral vectors, the pharmaceutical preparation can include one or more cells that produce the gene delivery system.

The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

15 Screening and Detection Methods

The isolated nucleic acid molecules of the invention can be used to express NOVX protein (*e.g.*, via a recombinant expression vector in a host cell in gene therapy applications), to detect NOVX mRNA (*e.g.*, in a biological sample) or a genetic lesion in an NOVX gene, and to modulate NOVX activity, as described further, below. In addition, the NOVX proteins can be used to screen drugs or compounds that modulate the NOVX protein activity or expression as well as to treat disorders characterized by insufficient or excessive production of NOVX protein or production of NOVX protein forms that have decreased or aberrant activity compared to NOVX wild-type protein (*e.g.*; diabetes (regulates insulin release); obesity (binds and transport lipids); metabolic disturbances associated with obesity, the metabolic syndrome X as well as anorexia and wasting disorders associated with chronic diseases and various cancers, and infectious disease (possesses anti-microbial activity) and the various dyslipidemias. In addition, the anti-NOVX antibodies of the invention can be used to detect and isolate NOVX proteins and modulate NOVX activity. In yet a further aspect, the invention can be used in methods to influence appetite, absorption of nutrients and the disposition of metabolic substrates in both a positive and negative fashion.

The invention further pertains to novel agents identified by the screening assays described herein and uses thereof for treatments as described, *supra*.

Screening Assays

5 The invention provides a method (also referred to herein as a "screening assay") for identifying modulators, *i.e.*, candidate or test compounds or agents (*e.g.*, peptides, peptidomimetics, small molecules or other drugs) that bind to NOVX proteins or have a stimulatory or inhibitory effect on, *e.g.*, NOVX protein expression or NOVX protein activity. The invention also includes compounds identified in the screening assays described herein.

10 In one embodiment, the invention provides assays for screening candidate or test compounds which bind to or modulate the activity of the membrane-bound form of an NOVX protein or polypeptide or biologically-active portion thereof. The test compounds of the invention can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the "one-bead one-compound"
15 library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds. *See, e.g.*, Lam, 1997. *Anticancer Drug Design* 12: 145.

20 A "small molecule" as used herein, is meant to refer to a composition that has a molecular weight of less than about 5 kD and most preferably less than about 4 kD. Small molecules can be, *e.g.*, nucleic acids, peptides, polypeptides, peptidomimetics, carbohydrates, lipids or other organic or inorganic molecules. Libraries of chemical and/or biological mixtures, such as fungal, bacterial, or algal extracts, are known in the art and can be screened with any of the assays of the invention.

25 Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt, *et al.*, 1993. *Proc. Natl. Acad. Sci. U.S.A.* 90: 6909; Erb, *et al.*, 1994. *Proc. Natl. Acad. Sci. U.S.A.* 91: 11422; Zuckermann, *et al.*, 1994. *J. Med. Chem.* 37: 2678; Cho, *et al.*, 1993. *Science* 261: 1303; Carrell, *et al.*, 1994. *Angew. Chem. Int. Ed. Engl.* 33: 2059; Carell, *et al.*, 1994. *Angew. Chem. Int. Ed. Engl.* 33: 2061; and Gallop, *et al.*, 1994. *J. Med. Chem.* 37:
30 1233.

Libraries of compounds may be presented in solution (*e.g.*, Houghten, 1992. *Biotechniques* 13: 412-421), or on beads (Lam, 1991. *Nature* 354: 82-84), on chips (Fodor, 1993. *Nature* 364: 555-556), bacteria (Ladner, U.S. Patent No. 5,223,409), spores (Ladner, U.S. Patent 5,233,409), plasmids (Cull, *et al.*, 1992. *Proc. Natl. Acad. Sci. USA* 89: 1865-1869) or on phage
5 (Scott and Smith, 1990. *Science* 249: 386-390; Devlin, 1990. *Science* 249: 404-406; Cwirla, *et al.*, 1990. *Proc. Natl. Acad. Sci. U.S.A.* 87: 6378-6382; Felici, 1991. *J. Mol. Biol.* 222: 301-310; Ladner, U.S. Patent No. 5,233,409.).

In one embodiment, an assay is a cell-based assay in which a cell which expresses a membrane-bound form of NOVX protein, or a biologically-active portion thereof, on the cell
10 surface is contacted with a test compound and the ability of the test compound to bind to an NOVX protein determined. The cell, for example, can be of mammalian origin or a yeast cell. Determining the ability of the test compound to bind to the NOVX protein can be accomplished, for example, by coupling the test compound with a radioisotope or enzymatic label such that
15 binding of the test compound to the NOVX protein or biologically-active portion thereof can be determined by detecting the labeled compound in a complex. For example, test compounds can be labeled with ^{125}I , ^{35}S , ^{14}C , or ^3H , either directly or indirectly, and the radioisotope detected by direct counting of radioemission or by scintillation counting. Alternatively, test compounds can be enzymatically-labeled with, for example, horseradish peroxidase, alkaline phosphatase, or
20 luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product. In one embodiment, the assay comprises contacting a cell which expresses a membrane-bound form of NOVX protein, or a biologically-active portion thereof, on the cell surface with a known compound which binds NOVX to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with an NOVX protein, wherein determining the ability of the test compound to interact with an
25 NOVX protein comprises determining the ability of the test compound to preferentially bind to NOVX protein or a biologically-active portion thereof as compared to the known compound.

In another embodiment, an assay is a cell-based assay comprising contacting a cell expressing a membrane-bound form of NOVX protein, or a biologically-active portion thereof, on the cell surface with a test compound and determining the ability of the test compound to
30 modulate (*e.g.*, stimulate or inhibit) the activity of the NOVX protein or biologically-active portion thereof. Determining the ability of the test compound to modulate the activity of NOVX

or a biologically-active portion thereof can be accomplished, for example, by determining the ability of the NOVX protein to bind to or interact with an NOVX target molecule. As used herein, a "target molecule" is a molecule with which an NOVX protein binds or interacts in nature, for example, a molecule on the surface of a cell which expresses an NOVX interacting protein, a molecule on the surface of a second cell, a molecule in the extracellular milieu, a molecule associated with the internal surface of a cell membrane or a cytoplasmic molecule. An NOVX target molecule can be a non-NOVX molecule or an NOVX protein or polypeptide of the invention. In one embodiment, an NOVX target molecule is a component of a signal transduction pathway that facilitates transduction of an extracellular signal (*e.g.* a signal generated by binding of a compound to a membrane-bound NOVX molecule) through the cell membrane and into the cell. The target, for example, can be a second intercellular protein that has catalytic activity or a protein that facilitates the association of downstream signaling molecules with NOVX.

Determining the ability of the NOVX protein to bind to or interact with an NOVX target molecule can be accomplished by one of the methods described above for determining direct binding. In one embodiment, determining the ability of the NOVX protein to bind to or interact with an NOVX target molecule can be accomplished by determining the activity of the target molecule. For example, the activity of the target molecule can be determined by detecting induction of a cellular second messenger of the target (*i.e.* intracellular Ca^{2+} , diacylglycerol, IP_3 , etc.), detecting catalytic/enzymatic activity of the target an appropriate substrate, detecting the induction of a reporter gene (comprising an NOVX-responsive regulatory element operatively linked to a nucleic acid encoding a detectable marker, *e.g.*, luciferase), or detecting a cellular response, for example, cell survival, cellular differentiation, or cell proliferation.

In yet another embodiment, an assay of the invention is a cell-free assay comprising contacting an NOVX protein or biologically-active portion thereof with a test compound and determining the ability of the test compound to bind to the NOVX protein or biologically-active portion thereof. Binding of the test compound to the NOVX protein can be determined either directly or indirectly as described above. In one such embodiment, the assay comprises contacting the NOVX protein or biologically-active portion thereof with a known compound which binds NOVX to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with an NOVX protein, wherein determining the ability of the test compound to interact with an NOVX protein comprises

determining the ability of the test compound to preferentially bind to NOVX or biologically-active portion thereof as compared to the known compound.

In still another embodiment, an assay is a cell-free assay comprising contacting NOVX protein or biologically-active portion thereof with a test compound and determining the ability of the test compound to modulate (*e.g.* stimulate or inhibit) the activity of the NOVX protein or biologically-active portion thereof. Determining the ability of the test compound to modulate the activity of NOVX can be accomplished, for example, by determining the ability of the NOVX protein to bind to an NOVX target molecule by one of the methods described above for determining direct binding. In an alternative embodiment, determining the ability of the test compound to modulate the activity of NOVX protein can be accomplished by determining the ability of the NOVX protein further modulate an NOVX target molecule. For example, the catalytic/enzymatic activity of the target molecule on an appropriate substrate can be determined as described, *supra*.

In yet another embodiment, the cell-free assay comprises contacting the NOVX protein or biologically-active portion thereof with a known compound which binds NOVX protein to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with an NOVX protein, wherein determining the ability of the test compound to interact with an NOVX protein comprises determining the ability of the NOVX protein to preferentially bind to or modulate the activity of an NOVX target molecule.

The cell-free assays of the invention are amenable to use of both the soluble form or the membrane-bound form of NOVX protein. In the case of cell-free assays comprising the membrane-bound form of NOVX protein, it may be desirable to utilize a solubilizing agent such that the membrane-bound form of NOVX protein is maintained in solution. Examples of such solubilizing agents include non-ionic detergents such as n-octylglucoside, n-dodecylglucoside, n-dodecylmaltoside, octanoyl-N-methylglucamide, decanoyl-N-methylglucamide, Triton[®] X-100, Triton[®] X-114, Thesit[®], Isotridecypoly(ethylene glycol ether)_n, N-dodecyl--N,N-dimethyl-3-ammonio-1-propane sulfonate, 3-(3-cholamidopropyl) dimethylamminiol-1-propane sulfonate (CHAPS), or 3-(3-cholamidopropyl)dimethylamminiol-2-hydroxy-1-propane sulfonate (CHAPSO).

In more than one embodiment of the above assay methods of the invention, it may be desirable to immobilize either NOVX protein or its target molecule to facilitate separation of

complexed from uncomplexed forms of one or both of the proteins, as well as to accommodate automation of the assay. Binding of a test compound to NOVX protein, or interaction of NOVX protein with a target molecule in the presence and absence of a candidate compound, can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels
5 include microtiter plates, test tubes, and micro-centrifuge tubes. In one embodiment, a fusion protein can be provided that adds a domain that allows one or both of the proteins to be bound to a matrix. For example, GST-NOVX fusion proteins or GST-target fusion proteins can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtiter plates, that are then combined with the test compound or the test compound and either
10 the non-adsorbed target protein or NOVX protein, and the mixture is incubated under conditions conducive to complex formation (*e.g.*, at physiological conditions for salt and pH). Following incubation, the beads or microtiter plate wells are washed to remove any unbound components, the matrix immobilized in the case of beads, complex determined either directly or indirectly, for example, as described, *supra*. Alternatively, the complexes can be dissociated from the matrix,
15 and the level of NOVX protein binding or activity determined using standard techniques.

Other techniques for immobilizing proteins on matrices can also be used in the screening assays of the invention. For example, either the NOVX protein or its target molecule can be immobilized utilizing conjugation of biotin and streptavidin. Biotinylated NOVX protein or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques
20 well-known within the art (*e.g.*, biotinylation kit, Pierce Chemicals, Rockford, Ill.), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). Alternatively, antibodies reactive with NOVX protein or target molecules, but which do not interfere with binding of the NOVX protein to its target molecule, can be derivatized to the wells of the plate, and unbound target or NOVX protein trapped in the wells by antibody conjugation. Methods for
25 detecting such complexes, in addition to those described above for the GST-immobilized complexes, include immunodetection of complexes using antibodies reactive with the NOVX protein or target molecule, as well as enzyme-linked assays that rely on detecting an enzymatic activity associated with the NOVX protein or target molecule.

In another embodiment, modulators of NOVX protein expression are identified in a
30 method wherein a cell is contacted with a candidate compound and the expression of NOVX mRNA or protein in the cell is determined. The level of expression of NOVX mRNA or protein

in the presence of the candidate compound is compared to the level of expression of NOVX mRNA or protein in the absence of the candidate compound. The candidate compound can then be identified as a modulator of NOVX mRNA or protein expression based upon this comparison. For example, when expression of NOVX mRNA or protein is greater (*i.e.*, statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of NOVX mRNA or protein expression. Alternatively, when expression of NOVX mRNA or protein is less (statistically significantly less) in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of NOVX mRNA or protein expression. The level of NOVX mRNA or protein expression in the cells can be determined by methods described herein for detecting NOVX mRNA or protein.

In yet another aspect of the invention, the NOVX proteins can be used as "bait proteins" in a two-hybrid assay or three hybrid assay (*see, e.g.*, U.S. Patent No. 5,283,317; Zervos, *et al.*, 1993. *Cell* 72: 223-232; Madura, *et al.*, 1993. *J. Biol. Chem.* 268: 12046-12054; Bartel, *et al.*, 1993. *Biotechniques* 14: 920-924; Iwabuchi, *et al.*, 1993. *Oncogene* 8: 1693-1696; and Brent WO 94/10300), to identify other proteins that bind to or interact with NOVX ("NOVX-binding proteins" or "NOVX-bp") and modulate NOVX activity. Such NOVX-binding proteins are also likely to be involved in the propagation of signals by the NOVX proteins as, for example, upstream or downstream elements of the NOVX pathway.

The two-hybrid system is based on the modular nature of most transcription factors, which consist of separable DNA-binding and activation domains. Briefly, the assay utilizes two different DNA constructs. In one construct, the gene that codes for NOVX is fused to a gene encoding the DNA binding domain of a known transcription factor (*e.g.*, GAL-4). In the other construct, a DNA sequence, from a library of DNA sequences, that encodes an unidentified protein ("prey" or "sample") is fused to a gene that codes for the activation domain of the known transcription factor. If the "bait" and the "prey" proteins are able to interact, *in vivo*, forming an NOVX-dependent complex, the DNA-binding and activation domains of the transcription factor are brought into close proximity. This proximity allows transcription of a reporter gene (*e.g.*, LacZ) that is operably linked to a transcriptional regulatory site responsive to the transcription factor. Expression of the reporter gene can be detected and cell colonies containing the functional

transcription factor can be isolated and used to obtain the cloned gene that encodes the protein which interacts with NOVX.

The invention further pertains to novel agents identified by the aforementioned screening assays and uses thereof for treatments as described herein.

5 **Detection Assays**

Portions or fragments of the cDNA sequences identified herein (and the corresponding complete gene sequences) can be used in numerous ways as polynucleotide reagents. By way of example, and not of limitation, these sequences can be used to: (i) map their respective genes on a chromosome; and, thus, locate gene regions associated with genetic disease; (ii) identify an
10 individual from a minute biological sample (tissue typing); and (iii) aid in forensic identification of a biological sample. Some of these applications are described in the subsections, below.

Chromosome Mapping

Once the sequence (or a portion of the sequence) of a gene has been isolated, this sequence
15 can be used to map the location of the gene on a chromosome. This process is called chromosome mapping. Accordingly, portions or fragments of the NOVX sequences, SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37, or fragments or derivatives thereof, can be used to map the location of the NOVX genes, respectively, on a chromosome. The mapping of the NOVX sequences to chromosomes is an important first step in correlating these sequences
20 with genes associated with disease.

Briefly, NOVX genes can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp in length) from the NOVX sequences. Computer analysis of the NOVX sequences can be used to rapidly select primers that do not span more than one exon in the genomic DNA, thus complicating the amplification process. These primers can then be used for
25 PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to the NOVX sequences will yield an amplified fragment.

Somatic cell hybrids are prepared by fusing somatic cells from different mammals (*e.g.*, human and mouse cells). As hybrids of human and mouse cells grow and divide, they gradually
30 lose human chromosomes in random order, but retain the mouse chromosomes. By using media

in which mouse cells cannot grow, because they lack a particular enzyme, but in which human cells can, the one human chromosome that contains the gene encoding the needed enzyme will be retained. By using various media, panels of hybrid cell lines can be established. Each cell line in a panel contains either a single human chromosome or a small number of human chromosomes, and a full set of mouse chromosomes, allowing easy mapping of individual genes to specific human chromosomes. *See, e.g., D'Eustachio, et al., 1983. Science 220: 919-924.* Somatic cell hybrids containing only fragments of human chromosomes can also be produced by using human chromosomes with translocations and deletions.

PCR mapping of somatic cell hybrids is a rapid procedure for assigning a particular sequence to a particular chromosome. Three or more sequences can be assigned per day using a single thermal cycler. Using the NOVX sequences to design oligonucleotide primers, sub-localization can be achieved with panels of fragments from specific chromosomes.

Fluorescence *in situ* hybridization (FISH) of a DNA sequence to a metaphase chromosomal spread can further be used to provide a precise chromosomal location in one step. Chromosome spreads can be made using cells whose division has been blocked in metaphase by a chemical like colcemid that disrupts the mitotic spindle. The chromosomes can be treated briefly with trypsin, and then stained with Giemsa. A pattern of light and dark bands develops on each chromosome, so that the chromosomes can be identified individually. The FISH technique can be used with a DNA sequence as short as 500 or 600 bases. However, clones larger than 1,000 bases have a higher likelihood of binding to a unique chromosomal location with sufficient signal intensity for simple detection. Preferably 1,000 bases, and more preferably 2,000 bases, will suffice to get good results at a reasonable amount of time. For a review of this technique, *see, Verma, et al., HUMAN CHROMOSOMES: A MANUAL OF BASIC TECHNIQUES (Pergamon Press, New York 1988).*

Reagents for chromosome mapping can be used individually to mark a single chromosome or a single site on that chromosome, or panels of reagents can be used for marking multiple sites and/or multiple chromosomes. Reagents corresponding to noncoding regions of the genes actually are preferred for mapping purposes. Coding sequences are more likely to be conserved within gene families, thus increasing the chance of cross hybridizations during chromosomal mapping.

Once a sequence has been mapped to a precise chromosomal location, the physical position of the sequence on the chromosome can be correlated with genetic map data. Such data are found, *e.g.*, in McKusick, MENDELIAN INHERITANCE IN MAN, available on-line through Johns Hopkins University Welch Medical Library). The relationship between genes and disease,
5 mapped to the same chromosomal region, can then be identified through linkage analysis (co-inheritance of physically adjacent genes), described in, *e.g.*, Egeland, *et al.*, 1987. *Nature*, 325: 783-787.

Moreover, differences in the DNA sequences between individuals affected and unaffected with a disease associated with the NOVX gene, can be determined. If a mutation is observed in
10 some or all of the affected individuals but not in any unaffected individuals, then the mutation is likely to be the causative agent of the particular disease. Comparison of affected and unaffected individuals generally involves first looking for structural alterations in the chromosomes, such as deletions or translocations that are visible from chromosome spreads or detectable using PCR based on that DNA sequence. Ultimately, complete sequencing of genes from several individuals
15 can be performed to confirm the presence of a mutation and to distinguish mutations from polymorphisms.

Tissue Typing

The NOVX sequences of the invention can also be used to identify individuals from
20 minute biological samples. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identification. The sequences of the invention are useful as additional DNA markers for RFLP ("restriction fragment length polymorphisms," described in U.S. Patent No. 5,272,057).

Furthermore, the sequences of the invention can be used to provide an alternative
25 technique that determines the actual base-by-base DNA sequence of selected portions of an individual's genome. Thus, the NOVX sequences described herein can be used to prepare two PCR primers from the 5'- and 3'-termini of the sequences. These primers can then be used to amplify an individual's DNA and subsequently sequence it.

Panels of corresponding DNA sequences from individuals, prepared in this manner, can
30 provide unique individual identifications, as each individual will have a unique set of such DNA

sequences due to allelic differences. The sequences of the invention can be used to obtain such identification sequences from individuals and from tissue. The NOVX sequences of the invention uniquely represent portions of the human genome. Allelic variation occurs to some degree in the coding regions of these sequences, and to a greater degree in the noncoding regions. It is estimated that allelic variation between individual humans occurs with a frequency of about once per each 500 bases. Much of the allelic variation is due to single nucleotide polymorphisms (SNPs), which include restriction fragment length polymorphisms (RFLPs).

Each of the sequences described herein can, to some degree, be used as a standard against which DNA from an individual can be compared for identification purposes. Because greater numbers of polymorphisms occur in the noncoding regions, fewer sequences are necessary to differentiate individuals. The noncoding sequences can comfortably provide positive individual identification with a panel of perhaps 10 to 1,000 primers that each yield a noncoding amplified sequence of 100 bases. If predicted coding sequences, such as those in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37 are used, a more appropriate number of primers for positive individual identification would be 500-2,000.

Predictive Medicine

The invention also pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, pharmacogenomics, and monitoring clinical trials are used for prognostic (predictive) purposes to thereby treat an individual prophylactically. Accordingly, one aspect of the invention relates to diagnostic assays for determining NOVX protein and/or nucleic acid expression as well as NOVX activity, in the context of a biological sample (*e.g.*, blood, serum, cells, tissue) to thereby determine whether an individual is afflicted with a disease or disorder, or is at risk of developing a disorder, associated with aberrant NOVX expression or activity. The disorders include metabolic disorders, diabetes, obesity, infectious disease, anorexia, cancer-associated cachexia, cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, and hematopoietic disorders, and the various dyslipidemias, metabolic disturbances associated with obesity, the metabolic syndrome X and wasting disorders associated with chronic diseases and various cancers. The invention also provides for prognostic (or predictive) assays for determining whether an individual is at risk of developing a disorder

associated with NOVX protein, nucleic acid expression or activity. For example, mutations in an NOVX gene can be assayed in a biological sample. Such assays can be used for prognostic or predictive purpose to thereby prophylactically treat an individual prior to the onset of a disorder characterized by or associated with NOVX protein, nucleic acid expression, or biological activity.

5 Another aspect of the invention provides methods for determining NOVX protein, nucleic acid expression or activity in an individual to thereby select appropriate therapeutic or prophylactic agents for that individual (referred to herein as "pharmacogenomics"). Pharmacogenomics allows for the selection of agents (*e.g.*, drugs) for therapeutic or prophylactic treatment of an individual based on the genotype of the individual (*e.g.*, the genotype of the individual examined to determine the ability of the individual to respond to a particular agent.)

10 Yet another aspect of the invention pertains to monitoring the influence of agents (*e.g.*, drugs, compounds) on the expression or activity of NOVX in clinical trials.

These and other agents are described in further detail in the following sections.

Diagnostic Assays

15 An exemplary method for detecting the presence or absence of NOVX in a biological sample involves obtaining a biological sample from a test subject and contacting the biological sample with a compound or an agent capable of detecting NOVX protein or nucleic acid (*e.g.*, mRNA, genomic DNA) that encodes NOVX protein such that the presence of NOVX is detected in the biological sample. An agent for detecting NOVX mRNA or genomic DNA is a labeled

20 nucleic acid probe capable of hybridizing to NOVX mRNA or genomic DNA. The nucleic acid probe can be, for example, a full-length NOVX nucleic acid, such as the nucleic acid of SEQ ID NOS: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37, or a portion thereof, such as an oligonucleotide of at least 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to NOVX mRNA or genomic DNA.

25 Other suitable probes for use in the diagnostic assays of the invention are described herein.

An agent for detecting NOVX protein is an antibody capable of binding to NOVX protein, preferably an antibody with a detectable label. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (*e.g.*, Fab or F(ab')₂) can be used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of

30 the probe or antibody by coupling (*i.e.*, physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent

that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently-labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently-labeled streptavidin. The term "biological sample" is intended to include tissues, cells and biological fluids isolated from a subject, as well as tissues, cells and fluids present within a subject. That is, the detection method of the invention can be used to detect NOVX mRNA, protein, or genomic DNA in a biological sample *in vitro* as well as *in vivo*. For example, *in vitro* techniques for detection of NOVX mRNA include Northern hybridizations and *in situ* hybridizations. *In vitro* techniques for detection of NOVX protein include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations, and immunofluorescence. *In vitro* techniques for detection of NOVX genomic DNA include Southern hybridizations. Furthermore, *in vivo* techniques for detection of NOVX protein include introducing into a subject a labeled anti-NOVX antibody. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

In one embodiment, the biological sample contains protein molecules from the test subject. Alternatively, the biological sample can contain mRNA molecules from the test subject or genomic DNA molecules from the test subject. A preferred biological sample is a peripheral blood leukocyte sample isolated by conventional means from a subject.

In another embodiment, the methods further involve obtaining a control biological sample from a control subject, contacting the control sample with a compound or agent capable of detecting NOVX protein, mRNA, or genomic DNA, such that the presence of NOVX protein, mRNA or genomic DNA is detected in the biological sample, and comparing the presence of NOVX protein, mRNA or genomic DNA in the control sample with the presence of NOVX protein, mRNA or genomic DNA in the test sample.

The invention also encompasses kits for detecting the presence of NOVX in a biological sample. For example, the kit can comprise: a labeled compound or agent capable of detecting NOVX protein or mRNA in a biological sample; means for determining the amount of NOVX in the sample; and means for comparing the amount of NOVX in the sample with a standard. The compound or agent can be packaged in a suitable container. The kit can further comprise instructions for using the kit to detect NOVX protein or nucleic acid.

Prognostic Assays

The diagnostic methods described herein can furthermore be utilized to identify subjects having or at risk of developing a disease or disorder associated with aberrant NOVX expression or activity. For example, the assays described herein, such as the preceding diagnostic assays or the following assays, can be utilized to identify a subject having or at risk of developing a disorder associated with NOVX protein, nucleic acid expression or activity. Alternatively, the prognostic assays can be utilized to identify a subject having or at risk for developing a disease or disorder. Thus, the invention provides a method for identifying a disease or disorder associated with aberrant NOVX expression or activity in which a test sample is obtained from a subject and NOVX protein or nucleic acid (*e.g.*, mRNA, genomic DNA) is detected, wherein the presence of NOVX protein or nucleic acid is diagnostic for a subject having or at risk of developing a disease or disorder associated with aberrant NOVX expression or activity. As used herein, a "test sample" refers to a biological sample obtained from a subject of interest. For example, a test sample can be a biological fluid (*e.g.*, serum), cell sample, or tissue.

Furthermore, the prognostic assays described herein can be used to determine whether a subject can be administered an agent (*e.g.*, an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate) to treat a disease or disorder associated with aberrant NOVX expression or activity. For example, such methods can be used to determine whether a subject can be effectively treated with an agent for a disorder. Thus, the invention provides methods for determining whether a subject can be effectively treated with an agent for a disorder associated with aberrant NOVX expression or activity in which a test sample is obtained and NOVX protein or nucleic acid is detected (*e.g.*, wherein the presence of NOVX protein or nucleic acid is diagnostic for a subject that can be administered the agent to treat a disorder associated with aberrant NOVX expression or activity).

The methods of the invention can also be used to detect genetic lesions in an NOVX gene, thereby determining if a subject with the lesioned gene is at risk for a disorder characterized by aberrant cell proliferation and/or differentiation. In various embodiments, the methods include detecting, in a sample of cells from the subject, the presence or absence of a genetic lesion characterized by at least one of an alteration affecting the integrity of a gene encoding an NOVX-protein, or the misexpression of the NOVX gene. For example, such genetic lesions can be detected by ascertaining the existence of at least one of: (i) a deletion of one or more

nucleotides from an NOVX gene; (ii) an addition of one or more nucleotides to an NOVX gene; (iii) a substitution of one or more nucleotides of an NOVX gene, (iv) a chromosomal rearrangement of an NOVX gene; (v) an alteration in the level of a messenger RNA transcript of an NOVX gene, (vi) aberrant modification of an NOVX gene, such as of the methylation pattern of the genomic DNA, (vii) the presence of a non-wild-type splicing pattern of a messenger RNA transcript of an NOVX gene, (viii) a non-wild-type level of an NOVX protein, (ix) allelic loss of an NOVX gene, and (x) inappropriate post-translational modification of an NOVX protein. As described herein, there are a large number of assay techniques known in the art which can be used for detecting lesions in an NOVX gene. A preferred biological sample is a peripheral blood leukocyte sample isolated by conventional means from a subject. However, any biological sample containing nucleated cells may be used, including, for example, buccal mucosal cells.

In certain embodiments, detection of the lesion involves the use of a probe/primer in a polymerase chain reaction (PCR) (*see, e.g.*, U.S. Patent Nos. 4,683,195 and 4,683,202), such as anchor PCR or RACE PCR, or, alternatively, in a ligation chain reaction (LCR) (*see, e.g.*, Landegran, *et al.*, 1988. *Science* 241: 1077-1080; and Nakazawa, *et al.*, 1994. *Proc. Natl. Acad. Sci. USA* 91: 360-364), the latter of which can be particularly useful for detecting point mutations in the NOVX-gene (*see*, Abravaya, *et al.*, 1995. *Nucl. Acids Res.* 23: 675-682). This method can include the steps of collecting a sample of cells from a patient, isolating nucleic acid (*e.g.*, genomic, mRNA or both) from the cells of the sample, contacting the nucleic acid sample with one or more primers that specifically hybridize to an NOVX gene under conditions such that hybridization and amplification of the NOVX gene (if present) occurs, and detecting the presence or absence of an amplification product, or detecting the size of the amplification product and comparing the length to a control sample. It is anticipated that PCR and/or LCR may be desirable to use as a preliminary amplification step in conjunction with any of the techniques used for detecting mutations described herein.

Alternative amplification methods include: self sustained sequence replication (*see*, Guatelli, *et al.*, 1990. *Proc. Natl. Acad. Sci. USA* 87: 1874-1878), transcriptional amplification system (*see*, Kwoh, *et al.*, 1989. *Proc. Natl. Acad. Sci. USA* 86: 1173-1177); Q β Replicase (*see*, Lizardi, *et al.*, 1988. *BioTechnology* 6: 1197), or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of

skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers.

In an alternative embodiment, mutations in an NOVX gene from a sample cell can be identified by alterations in restriction enzyme cleavage patterns. For example, sample and control
5 DNA is isolated, amplified (optionally), digested with one or more restriction endonucleases, and fragment length sizes are determined by gel electrophoresis and compared. Differences in fragment length sizes between sample and control DNA indicates mutations in the sample DNA. Moreover, the use of sequence specific ribozymes (*see, e.g.*, U.S. Patent No. 5,493,531) can be used to score for the presence of specific mutations by development or loss of a ribozyme
10 cleavage site.

In other embodiments, genetic mutations in NOVX can be identified by hybridizing a sample and control nucleic acids, *e.g.*, DNA or RNA, to high-density arrays containing hundreds or thousands of oligonucleotides probes. *See, e.g.*, Cronin, *et al.*, 1996. *Human Mutation* 7: 244-255; Kozal, *et al.*, 1996. *Nat. Med.* 2: 753-759. For example, genetic mutations in NOVX
15 can be identified in two dimensional arrays containing light-generated DNA probes as described in Cronin, *et al.*, *supra*. Briefly, a first hybridization array of probes can be used to scan through long stretches of DNA in a sample and control to identify base changes between the sequences by making linear arrays of sequential overlapping probes. This step allows the identification of point mutations. This is followed by a second hybridization array that allows the characterization of
20 specific mutations by using smaller, specialized probe arrays complementary to all variants or mutations detected. Each mutation array is composed of parallel probe sets, one complementary to the wild-type gene and the other complementary to the mutant gene.

In yet another embodiment, any of a variety of sequencing reactions known in the art can be used to directly sequence the NOVX gene and detect mutations by comparing the sequence of
25 the sample NOVX with the corresponding wild-type (control) sequence. Examples of sequencing reactions include those based on techniques developed by Maxim and Gilbert, 1977. *Proc. Natl. Acad. Sci. USA* 74: 560 or Sanger, 1977. *Proc. Natl. Acad. Sci. USA* 74: 5463. It is also contemplated that any of a variety of automated sequencing procedures can be utilized when performing the diagnostic assays (*see, e.g.*, Naeve, *et al.*, 1995. *Biotechniques* 19: 448), including
30 sequencing by mass spectrometry (*see, e.g.*, PCT International Publication No. WO 94/16101;

Cohen, *et al.*, 1996. *Adv. Chromatography* 36: 127-162; and Griffin, *et al.*, 1993. *Appl. Biochem. Biotechnol.* 38: 147-159).

Other methods for detecting mutations in the NOVX gene include methods in which protection from cleavage agents is used to detect mismatched bases in RNA/RNA or RNA/DNA heteroduplexes. *See, e.g.*, Myers, *et al.*, 1985. *Science* 230: 1242. In general, the art technique of "mismatch cleavage" starts by providing heteroduplexes of formed by hybridizing (labeled) RNA or DNA containing the wild-type NOVX sequence with potentially mutant RNA or DNA obtained from a tissue sample. The double-stranded duplexes are treated with an agent that cleaves single-stranded regions of the duplex such as which will exist due to basepair mismatches between the control and sample strands. For instance, RNA/DNA duplexes can be treated with RNase and DNA/DNA hybrids treated with S₁ nuclease to enzymatically digesting the mismatched regions. In other embodiments, either DNA/DNA or RNA/DNA duplexes can be treated with hydroxylamine or osmium tetroxide and with piperidine in order to digest mismatched regions. After digestion of the mismatched regions, the resulting material is then separated by size on denaturing polyacrylamide gels to determine the site of mutation. *See, e.g.*, Cotton, *et al.*, 1988. *Proc. Natl. Acad. Sci. USA* 85: 4397; Saleeba, *et al.*, 1992. *Methods Enzymol.* 217: 286-295. In an embodiment, the control DNA or RNA can be labeled for detection.

In still another embodiment, the mismatch cleavage reaction employs one or more proteins that recognize mismatched base pairs in double-stranded DNA (so called "DNA mismatch repair" enzymes) in defined systems for detecting and mapping point mutations in NOVX cDNAs obtained from samples of cells. For example, the mutY enzyme of *E. coli* cleaves A at G/A mismatches and the thymidine DNA glycosylase from HeLa cells cleaves T at G/T mismatches. *See, e.g.*, Hsu, *et al.*, 1994. *Carcinogenesis* 15: 1657-1662. According to an exemplary embodiment, a probe based on an NOVX sequence, *e.g.*, a wild-type NOVX sequence, is hybridized to a cDNA or other DNA product from a test cell(s). The duplex is treated with a DNA mismatch repair enzyme, and the cleavage products, if any, can be detected from electrophoresis protocols or the like. *See, e.g.*, U.S. Patent No. 5,459,039.

In other embodiments, alterations in electrophoretic mobility will be used to identify mutations in NOVX genes. For example, single strand conformation polymorphism (SSCP) may be used to detect differences in electrophoretic mobility between mutant and wild type nucleic acids. *See, e.g.*, Orita, *et al.*, 1989. *Proc. Natl. Acad. Sci. USA*: 86: 2766; Cotton, 1993. *Mutat.*

Res. 285: 125-144; Hayashi, 1992. *Genet. Anal. Tech. Appl.* 9: 73-79. Single-stranded DNA fragments of sample and control NOVX nucleic acids will be denatured and allowed to renature. The secondary structure of single-stranded nucleic acids varies according to sequence, the resulting alteration in electrophoretic mobility enables the detection of even a single base change.

5 The DNA fragments may be labeled or detected with labeled probes. The sensitivity of the assay may be enhanced by using RNA (rather than DNA), in which the secondary structure is more sensitive to a change in sequence. In one embodiment, the subject method utilizes heteroduplex analysis to separate double stranded heteroduplex molecules on the basis of changes in electrophoretic mobility. *See, e.g., Keen, et al., 1991. Trends Genet.* 7: 5.

10 In yet another embodiment, the movement of mutant or wild-type fragments in polyacrylamide gels containing a gradient of denaturant is assayed using denaturing gradient gel electrophoresis (DGGE). *See, e.g., Myers, et al., 1985. Nature* 313: 495. When DGGE is used as the method of analysis, DNA will be modified to insure that it does not completely denature, for example by adding a GC clamp of approximately 40 bp of high-melting GC-rich DNA by PCR.

15 In a further embodiment, a temperature gradient is used in place of a denaturing gradient to identify differences in the mobility of control and sample DNA. *See, e.g., Rosenbaum and Reissner, 1987. Biophys. Chem.* 265: 12753.

Examples of other techniques for detecting point mutations include, but are not limited to, selective oligonucleotide hybridization, selective amplification, or selective primer extension. For

20 example, oligonucleotide primers may be prepared in which the known mutation is placed centrally and then hybridized to target DNA under conditions that permit hybridization only if a perfect match is found. *See, e.g., Saiki, et al., 1986. Nature* 324: 163; Saiki, et al., 1989. *Proc. Natl. Acad. Sci. USA* 86: 6230. Such allele specific oligonucleotides are hybridized to PCR amplified target DNA or a number of different mutations when the oligonucleotides are attached

25 to the hybridizing membrane and hybridized with labeled target DNA.

Alternatively, allele specific amplification technology that depends on selective PCR amplification may be used in conjunction with the instant invention. Oligonucleotides used as primers for specific amplification may carry the mutation of interest in the center of the molecule (so that amplification depends on differential hybridization; *see, e.g., Gibbs, et al., 1989. Nucl.*

30 *Acids Res.* 17: 2437-2448) or at the extreme 3'-terminus of one primer where, under appropriate conditions, mismatch can prevent, or reduce polymerase extension (*see, e.g., Prossner, 1993.*

Tibtech. 11:238). In addition it may be desirable to introduce a novel restriction site in the region of the mutation to create cleavage-based detection. *See, e.g., Gasparini, et al., 1992. Mol. Cell Probes* 6: 1. It is anticipated that in certain embodiments amplification may also be performed using *Taq* ligase for amplification. *See, e.g., Barany, 1991. Proc. Natl. Acad. Sci. USA* 88: 189.

5 In such cases, ligation will occur only if there is a perfect match at the 3'-terminus of the 5' sequence, making it possible to detect the presence of a known mutation at a specific site by looking for the presence or absence of amplification.

The methods described herein may be performed, for example, by utilizing pre-packaged diagnostic kits comprising at least one probe nucleic acid or antibody reagent described herein,
10 which may be conveniently used, *e.g.,* in clinical settings to diagnose patients exhibiting symptoms or family history of a disease or illness involving an NOVX gene.

Furthermore, any cell type or tissue, preferably peripheral blood leukocytes, in which NOVX is expressed may be utilized in the prognostic assays described herein. However, any biological sample containing nucleated cells may be used, including, for example, buccal mucosal
15 cells.

Pharmacogenomics

Agents, or modulators that have a stimulatory or inhibitory effect on NOVX activity (*e.g.,* NOVX gene expression), as identified by a screening assay described herein can be administered to individuals to treat (prophylactically or therapeutically) disorders (The disorders include
20 metabolic disorders, diabetes, obesity, infectious disease, anorexia, cancer-associated cachexia, cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, and hematopoietic disorders, and the various dyslipidemias, metabolic disturbances associated with obesity, the metabolic syndrome X and wasting disorders associated with chronic diseases and various cancers.) In conjunction with such treatment, the pharmacogenomics (*i.e.,*
25 the study of the relationship between an individual's genotype and that individual's response to a foreign compound or drug) of the individual may be considered. Differences in metabolism of therapeutics can lead to severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug. Thus, the pharmacogenomics of the individual permits the selection of effective agents (*e.g.,* drugs) for prophylactic or therapeutic
30 treatments based on a consideration of the individual's genotype. Such pharmacogenomics can further be used to determine appropriate dosages and therapeutic regimens. Accordingly, the

activity of NOVX protein, expression of NOVX nucleic acid, or mutation content of NOVX genes in an individual can be determined to thereby select appropriate agent(s) for therapeutic or prophylactic treatment of the individual.

Pharmacogenomics deals with clinically significant hereditary variations in the response to drugs due to altered drug disposition and abnormal action in affected persons. See *e.g.*, Eichelbaum, 1996. *Clin. Exp. Pharmacol. Physiol.*, 23: 983-985; Linder, 1997. *Clin. Chem.*, 43: 254-266. In general, two types of pharmacogenetic conditions can be differentiated. Genetic conditions transmitted as a single factor altering the way drugs act on the body (altered drug action) or genetic conditions transmitted as single factors altering the way the body acts on drugs (altered drug metabolism). These pharmacogenetic conditions can occur either as rare defects or as polymorphisms. For example, glucose-6-phosphate dehydrogenase (G6PD) deficiency is a common inherited enzymopathy in which the main clinical complication is hemolysis after ingestion of oxidant drugs (anti-malarials, sulfonamides, analgesics, nitrofurans) and consumption of fava beans.

As an illustrative embodiment, the activity of drug metabolizing enzymes is a major determinant of both the intensity and duration of drug action. The discovery of genetic polymorphisms of drug metabolizing enzymes (*e.g.*, N-acetyltransferase 2 (NAT 2) and cytochrome P450 enzymes CYP2D6 and CYP2C19) has provided an explanation as to why some patients do not obtain the expected drug effects or show exaggerated drug response and serious toxicity after taking the standard and safe dose of a drug. These polymorphisms are expressed in two phenotypes in the population, the extensive metabolizer (EM) and poor metabolizer (PM). The prevalence of PM is different among different populations. For example, the gene coding for CYP2D6 is highly polymorphic and several mutations have been identified in PM, which all lead to the absence of functional CYP2D6. Poor metabolizers of CYP2D6 and CYP2C19 quite frequently experience exaggerated drug response and side effects when they receive standard doses. If a metabolite is the active therapeutic moiety, PM show no therapeutic response, as demonstrated for the analgesic effect of codeine mediated by its CYP2D6-formed metabolite morphine. At the other extreme are the so called ultra-rapid metabolizers who do not respond to standard doses. Recently, the molecular basis of ultra-rapid metabolism has been identified to be due to CYP2D6 gene amplification.

Thus, the activity of NOVX protein, expression of NOVX nucleic acid, or mutation content of NOVX genes in an individual can be determined to thereby select appropriate agent(s) for therapeutic or prophylactic treatment of the individual. In addition, pharmacogenetic studies can be used to apply genotyping of polymorphic alleles encoding drug-metabolizing enzymes to the identification of an individual's drug responsiveness phenotype. This knowledge, when applied to dosing or drug selection, can avoid adverse reactions or therapeutic failure and thus enhance therapeutic or prophylactic efficiency when treating a subject with an NOVX modulator, such as a modulator identified by one of the exemplary screening assays described herein.

Monitoring of Effects During Clinical Trials

Monitoring the influence of agents (*e.g.*, drugs, compounds) on the expression or activity of NOVX (*e.g.*, the ability to modulate aberrant cell proliferation and/or differentiation) can be applied not only in basic drug screening, but also in clinical trials. For example, the effectiveness of an agent determined by a screening assay as described herein to increase NOVX gene expression, protein levels, or upregulate NOVX activity, can be monitored in clinical trials of subjects exhibiting decreased NOVX gene expression, protein levels, or downregulated NOVX activity. Alternatively, the effectiveness of an agent determined by a screening assay to decrease NOVX gene expression, protein levels, or downregulate NOVX activity, can be monitored in clinical trials of subjects exhibiting increased NOVX gene expression, protein levels, or upregulated NOVX activity. In such clinical trials, the expression or activity of NOVX and, preferably, other genes that have been implicated in, for example, a cellular proliferation or immune disorder can be used as a "read out" or markers of the immune responsiveness of a particular cell.

By way of example, and not of limitation, genes, including NOVX, that are modulated in cells by treatment with an agent (*e.g.*, compound, drug or small molecule) that modulates NOVX activity (*e.g.*, identified in a screening assay as described herein) can be identified. Thus, to study the effect of agents on cellular proliferation disorders, for example, in a clinical trial, cells can be isolated and RNA prepared and analyzed for the levels of expression of NOVX and other genes implicated in the disorder. The levels of gene expression (*i.e.*, a gene expression pattern) can be quantified by Northern blot analysis or RT-PCR, as described herein, or alternatively by measuring the amount of protein produced, by one of the methods as described herein, or by measuring the levels of activity of NOVX or other genes. In this manner, the gene expression

pattern can serve as a marker, indicative of the physiological response of the cells to the agent. Accordingly, this response state may be determined before, and at various points during, treatment of the individual with the agent.

In one embodiment, the invention provides a method for monitoring the effectiveness of treatment of a subject with an agent (*e.g.*, an agonist, antagonist, protein, peptide, peptidomimetic, nucleic acid, small molecule, or other drug candidate identified by the screening assays described herein) comprising the steps of (i) obtaining a pre-administration sample from a subject prior to administration of the agent; (ii) detecting the level of expression of an NOVX protein, mRNA, or genomic DNA in the preadministration sample; (iii) obtaining one or more post-administration samples from the subject; (iv) detecting the level of expression or activity of the NOVX protein, mRNA, or genomic DNA in the post-administration samples; (v) comparing the level of expression or activity of the NOVX protein, mRNA, or genomic DNA in the pre-administration sample with the NOVX protein, mRNA, or genomic DNA in the post administration sample or samples; and (vi) altering the administration of the agent to the subject accordingly. For example, increased administration of the agent may be desirable to increase the expression or activity of NOVX to higher levels than detected, *i.e.*, to increase the effectiveness of the agent. Alternatively, decreased administration of the agent may be desirable to decrease expression or activity of NOVX to lower levels than detected, *i.e.*, to decrease the effectiveness of the agent.

20 Methods of Treatment

The invention provides for both prophylactic and therapeutic methods of treating a subject at risk of (or susceptible to) a disorder or having a disorder associated with aberrant NOVX expression or activity. The disorders include cardiomyopathy, atherosclerosis, hypertension, congenital heart defects, aortic stenosis, atrial septal defect (ASD), atrioventricular (A-V) canal defect, ductus arteriosus, pulmonary stenosis, subaortic stenosis, ventricular septal defect (VSD), valve diseases, tuberous sclerosis, scleroderma, obesity, transplantation, adrenoleukodystrophy, congenital adrenal hyperplasia, prostate cancer, neoplasm; adenocarcinoma, lymphoma, uterus cancer, fertility, hemophilia, hypercoagulation, idiopathic thrombocytopenic purpura, immunodeficiencies, graft versus host disease, AIDS, bronchial asthma, Crohn's disease; multiple

sclerosis, treatment of Albright Hereditary Osteodystrophy, and other diseases, disorders and conditions of the like.

These methods of treatment will be discussed more fully, below.

Disease and Disorders

5 Diseases and disorders that are characterized by increased (relative to a subject not suffering from the disease or disorder) levels or biological activity may be treated with Therapeutics that antagonize (*i.e.*, reduce or inhibit) activity. Therapeutics that antagonize activity may be administered in a therapeutic or prophylactic manner. Therapeutics that may be utilized include, but are not limited to: (i) an aforementioned peptide, or analogs, derivatives,
10 fragments or homologs thereof; (ii) antibodies to an aforementioned peptide; (iii) nucleic acids encoding an aforementioned peptide; (iv) administration of antisense nucleic acid and nucleic acids that are "dysfunctional" (*i.e.*, due to a heterologous insertion within the coding sequences of coding sequences to an aforementioned peptide) that are utilized to "knockout" endogenous function of an aforementioned peptide by homologous recombination (*see, e.g.*, Capecchi, 1989.
15 *Science* 244: 1288-1292); or (v) modulators (*i.e.*, inhibitors, agonists and antagonists, including additional peptide mimetic of the invention or antibodies specific to a peptide of the invention) that alter the interaction between an aforementioned peptide and its binding partner.

Diseases and disorders that are characterized by decreased (relative to a subject not suffering from the disease or disorder) levels or biological activity may be treated with
20 Therapeutics that increase (*i.e.*, are agonists to) activity. Therapeutics that upregulate activity may be administered in a therapeutic or prophylactic manner. Therapeutics that may be utilized include, but are not limited to, an aforementioned peptide, or analogs, derivatives, fragments or homologs thereof; or an agonist that increases bioavailability.

Increased or decreased levels can be readily detected by quantifying peptide and/or RNA,
25 by obtaining a patient tissue sample (*e.g.*, from biopsy tissue) and assaying it *in vitro* for RNA or peptide levels, structure and/or activity of the expressed peptides (or mRNAs of an aforementioned peptide). Methods that are well-known within the art include, but are not limited to, immunoassays (*e.g.*, by Western blot analysis, immunoprecipitation followed by sodium dodecyl sulfate (SDS) polyacrylamide gel electrophoresis, immunocytochemistry, etc.) and/or
30 hybridization assays to detect expression of mRNAs (*e.g.*, Northern assays, dot blots, *in situ* hybridization, and the like).

Prophylactic Methods

In one aspect, the invention provides a method for preventing, in a subject, a disease or condition associated with an aberrant NOVX expression or activity, by administering to the subject an agent that modulates NOVX expression or at least one NOVX activity. Subjects at risk for a disease that is caused or contributed to by aberrant NOVX expression or activity can be identified by, for example, any or a combination of diagnostic or prognostic assays as described herein. Administration of a prophylactic agent can occur prior to the manifestation of symptoms characteristic of the NOVX aberrancy, such that a disease or disorder is prevented or, alternatively, delayed in its progression. Depending upon the type of NOVX aberrancy, for example, an NOVX agonist or NOVX antagonist agent can be used for treating the subject. The appropriate agent can be determined based on screening assays described herein. The prophylactic methods of the invention are further discussed in the following subsections.

Therapeutic Methods

Another aspect of the invention pertains to methods of modulating NOVX expression or activity for therapeutic purposes. The modulatory method of the invention involves contacting a cell with an agent that modulates one or more of the activities of NOVX protein activity associated with the cell. An agent that modulates NOVX protein activity can be an agent as described herein, such as a nucleic acid or a protein, a naturally-occurring cognate ligand of an NOVX protein, a peptide, an NOVX peptidomimetic, or other small molecule. In one embodiment, the agent stimulates one or more NOVX protein activity. Examples of such stimulatory agents include active NOVX protein and a nucleic acid molecule encoding NOVX that has been introduced into the cell. In another embodiment, the agent inhibits one or more NOVX protein activity. Examples of such inhibitory agents include antisense NOVX nucleic acid molecules and anti-NOVX antibodies. These modulatory methods can be performed *in vitro* (e.g., by culturing the cell with the agent) or, alternatively, *in vivo* (e.g., by administering the agent to a subject). As such, the invention provides methods of treating an individual afflicted with a disease or disorder characterized by aberrant expression or activity of an NOVX protein or nucleic acid molecule. In one embodiment, the method involves administering an agent (e.g., an agent identified by a screening assay described herein), or combination of agents that modulates (e.g., up-regulates or down-regulates) NOVX expression or activity. In another embodiment, the

method involves administering an NOVX protein or nucleic acid molecule as therapy to compensate for reduced or aberrant NOVX expression or activity.

Stimulation of NOVX activity is desirable *in situations* in which NOVX is abnormally downregulated and/or in which increased NOVX activity is likely to have a beneficial effect. One example of such a situation is where a subject has a disorder characterized by aberrant cell proliferation and/or differentiation (*e.g.*, cancer or immune associated disorders). Another example of such a situation is where the subject has a gestational disease (*e.g.*, preclampsia).

Determination of the Biological Effect of the Therapeutic

In various embodiments of the invention, suitable *in vitro* or *in vivo* assays are performed to determine the effect of a specific Therapeutic and whether its administration is indicated for treatment of the affected tissue.

In various specific embodiments, *in vitro* assays may be performed with representative cells of the type(s) involved in the patient's disorder, to determine if a given Therapeutic exerts the desired effect upon the cell type(s). Compounds for use in therapy may be tested in suitable animal model systems including, but not limited to rats, mice, chicken, cows, monkeys, rabbits, and the like, prior to testing in human subjects. Similarly, for *in vivo* testing, any of the animal model system known in the art may be used prior to administration to human subjects.

Prophylactic and Therapeutic Uses of the Compositions of the Invention

The NOVX nucleic acids and proteins of the invention are useful in potential prophylactic and therapeutic applications implicated in a variety of disorders including, but not limited to: metabolic disorders, diabetes, obesity, infectious disease, anorexia, cancer-associated cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, hematopoietic disorders, and the various dyslipidemias, metabolic disturbances associated with obesity, the metabolic syndrome X and wasting disorders associated with chronic diseases and various cancers.

As an example, a cDNA encoding the NOVX protein of the invention may be useful in gene therapy, and the protein may be useful when administered to a subject in need thereof. By way of non-limiting example, the compositions of the invention will have efficacy for treatment of patients suffering from: metabolic disorders, diabetes, obesity, infectious disease, anorexia,

cancer-associated cachexia, cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, hematopoietic disorders, and the various dyslipidemias.

Both the novel nucleic acid encoding the NOVX protein, and the NOVX protein of the invention, or fragments thereof, may also be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed. A further use could be as an anti-bacterial molecule (*i.e.*, some peptides have been found to possess anti-bacterial properties). These materials are further useful in the generation of antibodies, which immunospecifically-bind to the novel substances of the invention for use in therapeutic or diagnostic methods.

The invention will be further described in the following examples, which do not limit the scope of the invention described in the claims.

Examples

Example 1. Quantitative expression analysis of clones in various cells and tissues

The quantitative expression of various clones was assessed using microtiter plates containing RNA samples from a variety of normal and pathology-derived cells, cell lines and tissues using real time quantitative PCR (RTQ PCR). RTQ PCR was performed on an Applied Biosystems ABI PRISM® 7700 or an ABI PRISM® 7900 HT Sequence Detection System.

Various collections of samples are assembled on the plates, and referred to as Panel 1 (containing normal tissues and cancer cell lines), Panel 2 (containing samples derived from tissues from normal and cancer sources), Panel 3 (containing cancer cell lines), Panel 4 (containing cells and cell lines from normal tissues and cells related to inflammatory conditions), Panel 5D/5I (containing human tissues and cell lines with an emphasis on metabolic diseases),

AI_comprehensive_panel (containing normal tissue and samples from autoimmune diseases), Panel CNSD.01 (containing central nervous system samples from normal and diseased brains) and CNS_neurodegeneration_panel (containing samples from normal and Alzheimer's diseased brains).

RNA integrity from all samples is controlled for quality by visual assessment of agarose gel electropherograms using 28S and 18S ribosomal RNA staining intensity ratio as a guide (2:1 to 2.5:1 28s:18s) and the absence of low molecular weight RNAs that would be indicative of

degradation products. Samples are controlled against genomic DNA contamination by RTQ PCR reactions run in the absence of reverse transcriptase using probe and primer sets designed to amplify across the span of a single exon.

First, the RNA samples were normalized to reference nucleic acids such as constitutively expressed genes (for example, β -actin and GAPDH). Normalized RNA (5 μ l) was converted to cDNA and analyzed by RTQ-PCR using One Step RT-PCR Master Mix Reagents (Applied Biosystems; Catalog No. 4309169) and gene-specific primers according to the manufacturer's instructions.

In other cases, non-normalized RNA samples were converted to single strand cDNA (sscDNA) using Superscript II (Invitrogen Corporation; Catalog No. 18064-147) and random hexamers according to the manufacturer's instructions. Reactions containing up to 10 μ g of total RNA were performed in a volume of 20 μ l and incubated for 60 minutes at 42°C. This reaction can be scaled up to 50 μ g of total RNA in a final volume of 100 μ l. sscDNA samples are then normalized to reference nucleic acids as described previously, using 1X TaqMan® Universal Master mix (Applied Biosystems; catalog No. 4324020), following the manufacturer's instructions.

Probes and primers were designed for each assay according to Applied Biosystems Primer Express Software package (version I for Apple Computer's Macintosh Power PC) or a similar algorithm using the target sequence as input. Default settings were used for reaction conditions and the following parameters were set before selecting primers: primer concentration = 250 nM, primer melting temperature (T_m) range = 58°-60°C, primer optimal T_m = 59°C, maximum primer difference = 2°C, probe does not have 5'G, probe T_m must be 10°C greater than primer T_m , amplicon size 75bp to 100bp. The probes and primers selected (see below) were synthesized by Synthegen (Houston, TX, USA). Probes were double purified by HPLC to remove uncoupled dye and evaluated by mass spectroscopy to verify coupling of reporter and quencher dyes to the 5' and 3' ends of the probe, respectively. Their final concentrations were: forward and reverse primers, 900nM each, and probe, 200nM.

PCR conditions: When working with RNA samples, normalized RNA from each tissue and each cell line was spotted in each well of either a 96 well or a 384-well PCR plate (Applied Biosystems). PCR cocktails included either a single gene specific probe and primers set, or two multiplexed probe and primers sets (a set specific for the target clone and another gene-specific

set multiplexed with the target probe). PCR reactions were set up using TaqMan® One-Step RT-PCR Master Mix (Applied Biosystems, Catalog No. 4313803) following manufacturer's instructions. Reverse transcription was performed at 48°C for 30 minutes followed by amplification/PCR cycles as follows: 95°C 10 min, then 40 cycles of 95°C for 15 seconds, 60°C for 1 minute. Results were recorded as CT values (cycle at which a given sample crosses a threshold level of fluorescence) using a log scale, with the difference in RNA concentration between a given sample and the sample with the lowest CT value being represented as 2 to the power of delta CT. The percent relative expression is then obtained by taking the reciprocal of this RNA difference and multiplying by 100.

When working with sscDNA samples, normalized sscDNA was used as described previously for RNA samples. PCR reactions containing one or two sets of probe and primers were set up as described previously, using 1X TaqMan® Universal Master mix (Applied Biosystems; catalog No. 4324020), following the manufacturer's instructions. PCR amplification was performed as follows: 95°C 10 min, then 40 cycles of 95°C for 15 seconds, 60°C for 1 minute. Results were analyzed and processed as described previously.

Panels 1, 1.1, 1.2, and 1.3D

The plates for Panels 1, 1.1, 1.2 and 1.3D include 2 control wells (genomic DNA control and chemistry control) and 94 wells containing cDNA from various samples. The samples in these panels are broken into 2 classes: samples derived from cultured cell lines and samples derived from primary normal tissues. The cell lines are derived from cancers of the following types: lung cancer, breast cancer, melanoma, colon cancer, prostate cancer, CNS cancer, squamous cell carcinoma, ovarian cancer, liver cancer, renal cancer, gastric cancer and pancreatic cancer. Cell lines used in these panels are widely available through the American Type Culture Collection (ATCC), a repository for cultured cell lines, and were cultured using the conditions recommended by the ATCC. The normal tissues found on these panels are comprised of samples derived from all major organ systems from single adult individuals or fetuses. These samples are derived from the following organs: adult skeletal muscle, fetal skeletal muscle, adult heart, fetal heart, adult kidney, fetal kidney, adult liver, fetal liver, adult lung, fetal lung, various regions of the brain, the spleen, bone marrow, lymph node, pancreas, salivary gland, pituitary gland, adrenal gland, spinal

cord, thymus, stomach, small intestine, colon, bladder, trachea, breast, ovary, uterus, placenta, prostate, testis and adipose.

In the results for Panels 1, 1.1, 1.2 and 1.3D, the following abbreviations are used:

ca. = carcinoma,

5 * = established from metastasis,

met = metastasis,

s cell var = small cell variant,

non-s = non-sm = non-small,

squam = squamous,

10 pl. eff = pl effusion = pleural effusion,

glio = glioma,

astro = astrocytoma, and

neuro = neuroblastoma.

General_screening_panel_v1.4

15 The plates for Panel 1.4 include 2 control wells (genomic DNA control and chemistry control) and 94 wells containing cDNA from various samples. The samples in Panel 1.4 are broken into 2 classes: samples derived from cultured cell lines and samples derived from primary normal tissues. The cell lines are derived from cancers of the following types: lung cancer, breast cancer, melanoma, colon cancer, prostate cancer, CNS cancer, squamous cell carcinoma, ovarian
20 cancer, liver cancer, renal cancer, gastric cancer and pancreatic cancer. Cell lines used in Panel 1.4 are widely available through the American Type Culture Collection (ATCC), a repository for cultured cell lines, and were cultured using the conditions recommended by the ATCC. The normal tissues found on Panel 1.4 are comprised of pools of samples derived from all major organ systems from 2 to 5 different adult individuals or fetuses. These samples are derived from the
25 following organs: adult skeletal muscle, fetal skeletal muscle, adult heart, fetal heart, adult kidney, fetal kidney, adult liver, fetal liver, adult lung, fetal lung, various regions of the brain, the spleen, bone marrow, lymph node, pancreas, salivary gland, pituitary gland, adrenal gland, spinal cord, thymus, stomach, small intestine, colon, bladder, trachea, breast, ovary, uterus, placenta, prostate, testis and adipose. Abbreviations are as described for Panels 1, 1.1, 1.2, and 1.3D.

Panels 2D and 2.2

The plates for Panels 2D and 2.2 generally include 2 control wells and 94 test samples composed of RNA or cDNA isolated from human tissue procured by surgeons working in close cooperation with the National Cancer Institute's Cooperative Human Tissue Network (CHTN) or the National Disease Research Initiative (NDRI). The tissues are derived from human malignancies and in cases where indicated many malignant tissues have "matched margins" obtained from noncancerous tissue just adjacent to the tumor. These are termed normal adjacent tissues and are denoted "NAT" in the results below. The tumor tissue and the "matched margins" are evaluated by two independent pathologists (the surgical pathologists and again by a pathologist at NDRI or CHTN). This analysis provides a gross histopathological assessment of tumor differentiation grade. Moreover, most samples include the original surgical pathology report that provides information regarding the clinical stage of the patient. These matched margins are taken from the tissue surrounding (i.e. immediately proximal) to the zone of surgery (designated "NAT", for normal adjacent tissue, in Table RR). In addition, RNA and cDNA samples were obtained from various human tissues derived from autopsies performed on elderly people or sudden death victims (accidents, etc.). These tissues were ascertained to be free of disease and were purchased from various commercial sources such as Clontech (Palo Alto, CA), Research Genetics, and Invitrogen.

Panel 3D

The plates of Panel 3D are comprised of 94 cDNA samples and two control samples. Specifically, 92 of these samples are derived from cultured human cancer cell lines, 2 samples of human primary cerebellar tissue and 2 controls. The human cell lines are generally obtained from ATCC (American Type Culture Collection), NCI or the German tumor cell bank and fall into the following tissue groups: Squamous cell carcinoma of the tongue, breast cancer, prostate cancer, melanoma, epidermoid carcinoma, sarcomas, bladder carcinomas, pancreatic cancers, kidney cancers, leukemias/lymphomas, ovarian/uterine/cervical, gastric, colon, lung and CNS cancer cell lines. In addition, there are two independent samples of cerebellum. These cells are all cultured under standard recommended conditions and RNA extracted using the standard procedures. The cell lines in panel 3D and 1.3D are of the most common cell lines used in the scientific literature.

Panels 4D, 4R, and 4.1D

Panel 4 includes samples on a 96 well plate (2 control wells, 94 test samples) composed of RNA (Panel 4R) or cDNA (Panels 4D/4.1D) isolated from various human cell lines or tissues related to inflammatory conditions. Total RNA from control normal tissues such as colon and lung (Stratagene, La Jolla, CA) and thymus and kidney (Clontech) was employed. Total RNA from liver tissue from cirrhosis patients and kidney from lupus patients was obtained from BioChain (Biochain Institute, Inc., Hayward, CA). Intestinal tissue for RNA preparation from patients diagnosed as having Crohn's disease and ulcerative colitis was obtained from the National Disease Research Interchange (NDRI) (Philadelphia, PA).

Astrocytes, lung fibroblasts, dermal fibroblasts, coronary artery smooth muscle cells, small airway epithelium, bronchial epithelium, microvascular dermal endothelial cells, microvascular lung endothelial cells, human pulmonary aortic endothelial cells, human umbilical vein endothelial cells were all purchased from Clonetics (Walkersville, MD) and grown in the media supplied for these cell types by Clonetics. These primary cell types were activated with various cytokines or combinations of cytokines for 6 and/or 12-14 hours, as indicated. The following cytokines were used; IL-1 beta at approximately 1-5ng/ml, TNF alpha at approximately 5-10ng/ml, IFN gamma at approximately 20-50ng/ml, IL-4 at approximately 5-10ng/ml, IL-9 at approximately 5-10ng/ml, IL-13 at approximately 5-10ng/ml. Endothelial cells were sometimes starved for various times by culture in the basal media from Clonetics with 0.1% serum.

Mononuclear cells were prepared from blood of employees at CuraGen Corporation, using Ficoll. LAK cells were prepared from these cells by culture in DMEM 5% FCS (Hyclone), 100µM non essential amino acids (Gibco/Life Technologies, Rockville, MD), 1mM sodium pyruvate (Gibco), mercaptoethanol 5.5×10^{-5} M (Gibco), and 10mM Hepes (Gibco) and Interleukin 2 for 4-6 days. Cells were then either activated with 10-20ng/ml PMA and 1-2µg/ml ionomycin, IL-12 at 5-10ng/ml, IFN gamma at 20-50ng/ml and IL-18 at 5-10ng/ml for 6 hours. In some cases, mononuclear cells were cultured for 4-5 days in DMEM 5% FCS (Hyclone), 100µM non essential amino acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol 5.5×10^{-5} M (Gibco), and 10mM Hepes (Gibco) with PHA (phytohemagglutinin) or PWM (pokeweed mitogen) at approximately 5µg/ml. Samples were taken at 24, 48 and 72 hours for RNA preparation. MLR (mixed lymphocyte reaction) samples were obtained by taking blood from two donors, isolating the mononuclear cells using Ficoll and mixing the isolated mononuclear cells 1:1 at a final

concentration of approximately 2×10^6 cells/ml in DMEM 5% FCS (Hyclone), $100 \mu\text{M}$ non essential amino acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol ($5.5 \times 10^{-5} \text{M}$) (Gibco), and 10mM Hepes (Gibco). The MLR was cultured and samples taken at various time points ranging from 1- 7 days for RNA preparation.

5 Monocytes were isolated from mononuclear cells using CD14 Miltenyi Beads, +ve VS selection columns and a Vario Magnet according to the manufacturer's instructions. Monocytes were differentiated into dendritic cells by culture in DMEM 5% fetal calf serum (FCS) (Hyclone, Logan, UT), $100 \mu\text{M}$ non essential amino acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol $5.5 \times 10^{-5} \text{M}$ (Gibco), and 10mM Hepes (Gibco), 50ng/ml GMCSF and 5ng/ml IL-4 for 5-7 days. Macrophages were prepared by culture of monocytes for 5-7 days in DMEM 10 5% FCS (Hyclone), $100 \mu\text{M}$ non essential amino acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol $5.5 \times 10^{-5} \text{M}$ (Gibco), 10mM Hepes (Gibco) and 10% AB Human Serum or MCSF at approximately 50ng/ml . Monocytes, macrophages and dendritic cells were stimulated for 6 and 12-14 hours with lipopolysaccharide (LPS) at 100ng/ml . Dendritic cells were also 15 stimulated with anti-CD40 monoclonal antibody (Pharmingen) at $10 \mu\text{g/ml}$ for 6 and 12-14 hours.

CD4 lymphocytes, CD8 lymphocytes and NK cells were also isolated from mononuclear cells using CD4, CD8 and CD56 Miltenyi beads, positive VS selection columns and a Vario Magnet according to the manufacturer's instructions. CD45RA and CD45RO CD4 lymphocytes were isolated by depleting mononuclear cells of CD8, CD56, CD14 and CD19 cells using CD8, 20 CD56, CD14 and CD19 Miltenyi beads and positive selection. CD45RO beads were then used to isolate the CD45RO CD4 lymphocytes with the remaining cells being CD45RA CD4 lymphocytes. CD45RA CD4, CD45RO CD4 and CD8 lymphocytes were placed in DMEM 5% FCS (Hyclone), $100 \mu\text{M}$ non essential amino acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol $5.5 \times 10^{-5} \text{M}$ (Gibco), and 10mM Hepes (Gibco) and plated at 10^6 cells/ml onto 25 Falcon 6 well tissue culture plates that had been coated overnight with $0.5 \mu\text{g/ml}$ anti-CD28 (Pharmingen) and $3 \mu\text{g/ml}$ anti-CD3 (OKT3, ATCC) in PBS. After 6 and 24 hours, the cells were harvested for RNA preparation. To prepare chronically activated CD8 lymphocytes, we activated the isolated CD8 lymphocytes for 4 days on anti-CD28 and anti-CD3 coated plates and then harvested the cells and expanded them in DMEM 5% FCS (Hyclone), $100 \mu\text{M}$ non essential amino 30 acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol $5.5 \times 10^{-5} \text{M}$ (Gibco), and 10mM Hepes (Gibco) and IL-2. The expanded CD8 cells were then activated again with plate bound

anti-CD3 and anti-CD28 for 4 days and expanded as before. RNA was isolated 6 and 24 hours after the second activation and after 4 days of the second expansion culture. The isolated NK cells were cultured in DMEM 5% FCS (Hyclone), 100µM non essential amino acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol 5.5x10-5M (Gibco), and 10mM Hepes (Gibco) and IL-2 for 4-6 days before RNA was prepared.

To obtain B cells, tonsils were procured from NDRI. The tonsil was cut up with sterile dissecting scissors and then passed through a sieve. Tonsil cells were then spun down and resuspended at 106cells/ml in DMEM 5% FCS (Hyclone), 100µM non essential amino acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol 5.5x10-5M (Gibco), and 10mM Hepes (Gibco). To activate the cells, we used PWM at 5µg/ml or anti-CD40 (Pharmingen) at approximately 10µg/ml and IL-4 at 5-10ng/ml. Cells were harvested for RNA preparation at 24, 48 and 72 hours.

To prepare the primary and secondary Th1/Th2 and Tr1 cells, six-well Falcon plates were coated overnight with 10µg/ml anti-CD28 (Pharmingen) and 2µg/ml OKT3 (ATCC), and then washed twice with PBS. Umbilical cord blood CD4 lymphocytes (Poietic Systems, German Town, MD) were cultured at 105-106cells/ml in DMEM 5% FCS (Hyclone), 100µM non essential amino acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol 5.5x10-5M (Gibco), 10mM Hepes (Gibco) and IL-2 (4ng/ml). IL-12 (5ng/ml) and anti-IL4 (1µg/ml) were used to direct to Th1, while IL-4 (5ng/ml) and anti-IFN gamma (1µg/ml) were used to direct to Th2 and IL-10 at 5ng/ml was used to direct to Tr1. After 4-5 days, the activated Th1, Th2 and Tr1 lymphocytes were washed once in DMEM and expanded for 4-7 days in DMEM 5% FCS (Hyclone), 100µM non essential amino acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol 5.5x10-5M (Gibco), 10mM Hepes (Gibco) and IL-2 (1ng/ml). Following this, the activated Th1, Th2 and Tr1 lymphocytes were re-stimulated for 5 days with anti-CD28/OKT3 and cytokines as described above, but with the addition of anti-CD95L (1µg/ml) to prevent apoptosis. After 4-5 days, the Th1, Th2 and Tr1 lymphocytes were washed and then expanded again with IL-2 for 4-7 days. Activated Th1 and Th2 lymphocytes were maintained in this way for a maximum of three cycles. RNA was prepared from primary and secondary Th1, Th2 and Tr1 after 6 and 24 hours following the second and third activations with plate bound anti-CD3 and anti-CD28 mAbs and 4 days into the second and third expansion cultures in Interleukin 2.

The following leukocyte cells lines were obtained from the ATCC: Ramos, EOL-1, KU-812. EOL cells were further differentiated by culture in 0.1mM dbcAMP at 5x10⁵cells/ml for 8 days, changing the media every 3 days and adjusting the cell concentration to 5x10⁵cells/ml. For the culture of these cells, we used DMEM or RPMI (as recommended by the ATCC), with the addition of 5% FCS (Hyclone), 100μM non essential amino acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol 5.5x10⁻⁵M (Gibco), 10mM Hepes (Gibco). RNA was either prepared from resting cells or cells activated with PMA at 10ng/ml and ionomycin at 1μg/ml for 6 and 14 hours. Keratinocyte line CCD106 and an airway epithelial tumor line NCI-H292 were also obtained from the ATCC. Both were cultured in DMEM 5% FCS (Hyclone), 100μM non essential amino acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol 5.5x10⁻⁵M (Gibco), and 10mM Hepes (Gibco). CCD1106 cells were activated for 6 and 14 hours with approximately 5 ng/ml TNF alpha and 1ng/ml IL-1 beta, while NCI-H292 cells were activated for 6 and 14 hours with the following cytokines: 5ng/ml IL-4, 5ng/ml IL-9, 5ng/ml IL-13 and 25ng/ml IFN gamma.

For these cell lines and blood cells, RNA was prepared by lysing approximately 10⁷cells/ml using Trizol (Gibco BRL). Briefly, 1/10 volume of bromochloropropane (Molecular Research Corporation) was added to the RNA sample, vortexed and after 10 minutes at room temperature, the tubes were spun at 14,000 rpm in a Sorvall SS34 rotor. The aqueous phase was removed and placed in a 15ml Falcon Tube. An equal volume of isopropanol was added and left at -20°C overnight. The precipitated RNA was spun down at 9,000 rpm for 15 min in a Sorvall SS34 rotor and washed in 70% ethanol. The pellet was redissolved in 300μl of RNase-free water and 35μl buffer (Promega) 5μl DTT, 7μl RNAsin and 8μl DNase were added. The tube was incubated at 37°C for 30 minutes to remove contaminating genomic DNA, extracted once with phenol chloroform and re-precipitated with 1/10 volume of 3M sodium acetate and 2 volumes of 100% ethanol. The RNA was spun down and placed in RNase free water. RNA was stored at -80°C.

AI_comprehensive panel_v1.0

The plates for AI_comprehensive panel_v1.0 include two control wells and 89 test samples comprised of cDNA isolated from surgical and postmortem human tissues obtained from the Backus Hospital and Clinomics (Frederick, MD). Total RNA was extracted from tissue samples from the Backus Hospital in the Facility at CuraGen. Total RNA from other tissues was obtained from Clinomics.

Joint tissues including synovial fluid, synovium, bone and cartilage were obtained from patients undergoing total knee or hip replacement surgery at the Backus Hospital. Tissue samples were immediately snap frozen in liquid nitrogen to ensure that isolated RNA was of optimal quality and not degraded. Additional samples of osteoarthritis and rheumatoid arthritis joint tissues were obtained from Clinomics. Normal control tissues were supplied by Clinomics and were obtained during autopsy of trauma victims.

Surgical specimens of psoriatic tissues and adjacent matched tissues were provided as total RNA by Clinomics. Two male and two female patients were selected between the ages of 25 and 47. None of the patients were taking prescription drugs at the time samples were isolated.

Surgical specimens of diseased colon from patients with ulcerative colitis and Crohns disease and adjacent matched tissues were obtained from Clinomics. Bowel tissue from three female and three male Crohn's patients between the ages of 41-69 were used. Two patients were not on prescription medication while the others were taking dexamethasone, phenobarbital, or tylenol. Ulcerative colitis tissue was from three male and four female patients. Four of the patients were taking lebid and two were on phenobarbital.

Total RNA from post mortem lung tissue from trauma victims with no disease or with emphysema, asthma or COPD was purchased from Clinomics. Emphysema patients ranged in age from 40-70 and all were smokers, this age range was chosen to focus on patients with cigarette-linked emphysema and to avoid those patients with alpha-1 anti-trypsin deficiencies. Asthma patients ranged in age from 36-75, and excluded smokers to prevent those patients that could also have COPD. COPD patients ranged in age from 35-80 and included both smokers and non-smokers. Most patients were taking corticosteroids, and bronchodilators.

In the labels employed to identify tissues in the AI_comprehensive panel_v1.0 panel, the following abbreviations are used:

AI = Autoimmunity

Syn = Synovial

Normal = No apparent disease

Rep22 /Rep20 = individual patients

RA = Rheumatoid arthritis

Backus = From Backus Hospital

OA = Osteoarthritis

(SS) (BA) (MF) = Individual patients

Adj = Adjacent tissue

Match control = adjacent tissues

-M = Male

-F = Female

COPD = Chronic obstructive pulmonary disease

Panels 5D and 5I

The plates for Panel 5D and 5I include two control wells and a variety of cDNAs isolated from human tissues and cell lines with an emphasis on metabolic diseases. Metabolic tissues were obtained from patients enrolled in the Gestational Diabetes study. Cells were obtained during different stages in the differentiation of adipocytes from human mesenchymal stem cells. Human pancreatic islets were also obtained.

In the Gestational Diabetes study subjects are young (18 - 40 years), otherwise healthy women with and without gestational diabetes undergoing routine (elective) Caesarean section. After delivery of the infant, when the surgical incisions were being repaired/closed, the obstetrician removed a small sample.

Patient 2: Diabetic Hispanic, overweight, not on insulin

Patient 7-9: Nondiabetic Caucasian and obese (BMI>30)

Patient 10: Diabetic Hispanic, overweight, on insulin

Patient 11: Nondiabetic African American and overweight

Patient 12: Diabetic Hispanic on insulin

Adipocyte differentiation was induced in donor progenitor cells obtained from Osirus (a division of Clonetics/BioWhittaker) in triplicate, except for Donor 3U which had only two replicates. Scientists at Clonetics isolated, grew and differentiated human mesenchymal stem cells (HuMSCs) for CuraGen based on the published protocol found in Mark F. Pittenger, et al., Multilineage Potential of Adult Human Mesenchymal Stem Cells Science Apr 2 1999: 143-147. Clonetics provided Trizol lysates or frozen pellets suitable for mRNA isolation and ds cDNA production. A general description of each donor is as follows:

Donor 2 and 3 U: Mesenchymal Stem cells, Undifferentiated Adipose

Donor 2 and 3 AM: Adipose, AdiposeMidway Differentiated

Donor 2 and 3 AD: Adipose, Adipose Differentiated

Human cell lines were generally obtained from ATCC (American Type Culture Collection), NCI or the German tumor cell bank and fall into the following tissue groups: kidney proximal convoluted tubule, uterine smooth muscle cells, small intestine, liver HepG2 cancer cells, heart primary stromal cells, and adrenal cortical adenoma cells. These cells are all cultured under standard recommended conditions and RNA extracted using the standard procedures. All samples were processed at CuraGen to produce single stranded cDNA.

Panel 5I contains all samples previously described with the addition of pancreatic islets from a 58 year old female patient obtained from the Diabetes Research Institute at the University of Miami School of Medicine. Islet tissue was processed to total RNA at an outside source and delivered to CuraGen for addition to panel 5I.

In the labels employed to identify tissues in the 5D and 5I panels, the following abbreviations are used:

GO Adipose = Greater Omentum Adipose

SK = Skeletal Muscle

UT = Uterus

PL = Placenta

AD = Adipose Differentiated

AM = Adipose Midway Differentiated

U = Undifferentiated Stem Cells

Panel CNSD.01

The plates for Panel CNSD.01 include two control wells and 94 test samples comprised of cDNA isolated from postmortem human brain tissue obtained from the Harvard Brain Tissue Resource Center. Brains are removed from calvaria of donors between 4 and 24 hours after death, sectioned by neuroanatomists, and frozen at -80°C in liquid nitrogen vapor. All brains are sectioned and examined by neuropathologists to confirm diagnoses with clear associated neuropathology.

Disease diagnoses are taken from patient records. The panel contains two brains from each of the following diagnoses: Alzheimer's disease, Parkinson's disease, Huntington's disease, Progressive Supranuclear Palsy, Depression, and "Normal controls". Within each of these brains, the following regions are represented: cingulate gyrus, temporal pole, globus pallidus, substantia

nigra, Brodman Area 4 (primary motor strip), Brodman Area 7 (parietal cortex), Brodman Area 9 (prefrontal cortex), and Brodman area 17 (occipital cortex). Not all brain regions are represented in all cases; e.g., Huntington's disease is characterized in part by neurodegeneration in the globus palladus, thus this region is impossible to obtain from confirmed Huntington's cases. Likewise
5 Parkinson's disease is characterized by degeneration of the substantia nigra making this region more difficult to obtain. Normal control brains were examined for neuropathology and found to be free of any pathology consistent with neurodegeneration.

In the labels employed to identify tissues in the CNS panel, the following abbreviations are used:

- 10 PSP = Progressive supranuclear palsy
- Sub Nigra = Substantia nigra
- Glob Palladus= Globus palladus
- Temp Pole = Temporal pole
- Cing Gyr = Cingulate gyrus
- 15 BA 4 = Brodman Area 4

Panel CNS_Neurodegeneration_V1.0

The plates for Panel CNS_Neurodegeneration_V1.0 include two control wells and 47 test samples comprised of cDNA isolated from postmortem human brain tissue obtained from the
20 Harvard Brain Tissue Resource Center (McLean Hospital) and the Human Brain and Spinal Fluid Resource Center (VA Greater Los Angeles Healthcare System). Brains are removed from calvaria of donors between 4 and 24 hours after death, sectioned by neuroanatomists, and frozen at -80°C in liquid nitrogen vapor. All brains are sectioned and examined by neuropathologists to confirm diagnoses with clear associated neuropathology.

- 25 Disease diagnoses are taken from patient records. The panel contains six brains from Alzheimer's disease (AD) patients, and eight brains from "Normal controls" who showed no evidence of dementia prior to death. The eight normal control brains are divided into two categories: Controls with no dementia and no Alzheimer's like pathology (Controls) and controls with no dementia but evidence of severe Alzheimer's like pathology, (specifically senile plaque
30 load rated as level 3 on a scale of 0-3; 0 = no evidence of plaques, 3 = severe AD senile plaque load). Within each of these brains, the following regions are represented: hippocampus, temporal

cortex (Brodman Area 21), parietal cortex (Brodman area 7), and occipital cortex (Brodman area 17). These regions were chosen to encompass all levels of neurodegeneration in AD. The hippocampus is a region of early and severe neuronal loss in AD; the temporal cortex is known to show neurodegeneration in AD after the hippocampus; the parietal cortex shows moderate neuronal death in the late stages of the disease; the occipital cortex is spared in AD and therefore acts as a "control" region within AD patients. Not all brain regions are represented in all cases.

In the labels employed to identify tissues in the CNS_Neurodegeneration_V1.0 panel, the following abbreviations are used:

AD = Alzheimer's disease brain; patient was demented and showed AD-like pathology upon autopsy

Control = Control brains; patient not demented, showing no neuropathology

Control (Path) = Control brains; patient not demented but showing severe AD-like pathology

SupTemporal Ctx = Superior Temporal Cortex

Inf Temporal Ctx = Inferior Temporal Cortex

NOV1a and NOV1b (AC084364.5/cg-AC084364.5 and 11400078/CG50736-10: Stabilin_like)

Expression of gene AC084364.5 and variant CG50736-10 was assessed using the primer-probe sets Ag03, Ag068, Ag812, Ag2742, Ag2743, Ag2744, Ag2745 and Ag2746, described in Tables AA, AB, AC, AD, AE, AF, AG, AH and AI. Results of the RTQ-PCR runs are shown in Tables AJ, AK, AL, AM and AN.

Table AA. Probe Name Ag03

Primers	Sequences	Length	Start Position
Forward	5'-ctggttgtaggttgccatggt-3' (SEQ ID NO:115)	21	7156
Probe	TET-5'-cagcttcggttgccacaggcctctc-3'-TAMRA (SEQ ID NO:116)	24	7130
Reverse	5'-ccagtataagctgacctttgacaaag-3' (SEQ ID NO:117)	26	7101

Table AB. Probe Name Ag068

Primers	Sequences	Length	Start Position
Forward	5'-ctggttgtaggttgccatggt-3' (SEQ ID NO:118)	21	7156
Probe	TET-5'-cagcttcgttggcacaggcctctc-3'-TAMRA (SEQ ID NO:119)	24	7130
Reverse	5'-ccagtataagctgacctttgacaaag-3' (SEQ ID NO:120)	26	7101

Table AC. Probe Name Ag793

Primers	Sequences	Length	Start Position
Forward	5'-ccaagggttttagctgtggatct-3' (SEQ ID NO:121)	22	5936
Probe	TET-5'-acatccactgcttgaagaccctg-3'-TAMRA (SEQ ID NO:122)	24	5962
Reverse	5'-cacatttcacactcagctctga-3' (SEQ ID NO:123)	22	5992

Table AD. Probe Name Ag812

Primers	Sequences	Length	Start Position
Forward	5'-caggagcatttcgtgaaaga-3' (SEQ ID NO:124)	20	5329
Probe	TET-5'-ttttgcacctttatctgcagcctttg-3'-TAMRA (SEQ ID NO:125)	26	5376
Reverse	5'-tttaaccgcagcttctcat-3' (SEQ ID NO:126)	20	5402

Table AE. Probe Name Ag2742

Primers	Sequences	Length	Start Position
Forward	5'-ctgcaaaatcttacgactttgg-3' (SEQ ID NO:127)	22	5701
Probe	TET-5'-caacaacaatggctacatcaaatttagca-3'-TAMRA (SEQ ID NO:128)	30	5723
Reverse	5'-atgacactcagcaaacctgagt-3' (SEQ ID NO:129)	22	5765

Table AF. Probe Name Ag2743

Primers	Sequences	Length	Start Position
Forward	5'-ctgcaaaatcttacgactttgg-3' (SEQ ID NO:130)	22	5701
Probe	TET-5'-caacaacaatggctacatcaaatttagca-3'-TAMRA (SEQ ID NO:131)	30	5723
Reverse	5'-atgacactcagcaaacctgagt-3' (SEQ ID NO:132)	22	5765

Table AG. Probe Name Ag2744

Primers	Sequences	Length	Start Position
Forward	5'-ctgcaaaatcttacgactttgg-3' (SEQ ID NO:133)	22	5701
Probe	TET-5'-caacaaacaatggctacatcaaatttagca-3'-TAMRA (SEQ ID NO:134)	30	5723
Reverse	5'-tcagcaaactgagtcctgta-3' (SEQ ID NO:135)	21	5759

Table AH. Probe Name Ag2745

Primers	Sequences	Length	Start Position
Forward	5'-ctgcaaaatcttacgactttgg-3' (SEQ ID NO:136)	22	5701
Probe	TET-5'-caacaaacaatggctacatcaaatttagca-3'-TAMRA (SEQ ID NO:137)	30	5723
Reverse	5'-atgacactcagcaaactgagt-3' (SEQ ID NO:138)	22	5765

Table AI. Probe Name Ag2746

Primers	Sequences	Length	Start Position
Forward	5'-ctgcaaaatcttacgactttgg-3' (SEQ ID NO:139)	22	5701
Probe	TET-5'-caacaaacaatggctacatcaaatttagca-3'-TAMRA (SEQ ID NO:140)	30	5723
Reverse	5'-atgacactcagcaaactgagt-3' (SEQ ID NO:141)	22	5765

Table AJ. Panel 1

Tissue Name	Rel. Exp.(%) Ag03, Run 87353672	Rel. Exp.(%) Ag068, Run 87361479	Tissue Name	Rel. Exp.(%) Ag03, Run 87353672	Rel. Exp.(%) Ag068, Run 87361479
Endothelial cells	0.0	0.0	Renal ca. 786-0	0.0	0.0
Endothelial cells (treated)	0.0	0.0	Renal ca. A498	0.1	0.5
Pancreas	0.0	2.3	Renal ca. RXF 393	0.0	0.0
Pancreatic ca. CAPAN 2	0.0	0.0	Renal ca. ACHN	0.0	0.0
Adrenal gland	0.5	1.3	Renal ca. UO- 31	0.0	0.1
Thyroid	1.8	2.1	Renal ca. TK-10	0.2	0.9
Salivary gland	2.5	3.0	Liver	14.2	12.9

Pituitary gland	0.8	0.8	Liver (fetal)	25.7	15.6
Brain (fetal)	0.1	0.4	Liver ca. (hepatoblast) HepG2	0.0	0.1
Brain (whole)	0.3	0.6	Lung	0.5	0.1
Brain (amygdala)	0.1	0.4	Lung (fetal)	4.4	6.2
Brain (cerebellum)	0.4	0.7	Lung ca. (small cell) LX-1	0.0	0.0
Brain (hippocampus)	0.3	0.9	Lung ca. (small cell) NCI-H69	0.1	0.4
Brain (substantia nigra)	0.1	0.3	Lung ca. (s.cell var.) SHP-77	0.0	0.0
Brain (thalamus)	0.1	0.2	Lung ca. (large cell) NCI-H460	0.0	0.0
Brain (hypothalamus)	0.4	0.5	Lung ca. (non- sm. cell) A549	0.0	0.1
Spinal cord	0.0	0.3	Lung ca. (non- s.cell) NCI-H23	0.0	0.3
glio/astro U87- MG	0.0	0.1	Lung ca. (non- s.cell) HOP-62	0.0	0.1
glio/astro U-118- MG	0.1	0.2	Lung ca. (non- s.cl) NCI-H522	0.0	0.0
astrocytoma SW1783	0.0	0.0	Lung ca. (squam.) SW 900	0.0	0.1
neuro*; met SK- N-AS	0.0	0.0	Lung ca. (squam.) NCI- H596	0.1	0.3
astrocytoma SF- 539	0.0	0.1	Mammary gland	4.7	5.1
astrocytoma SNB- 75	0.1	0.2	Breast ca.* (pl.ef) MCF-7	0.0	0.2
glioma SNB-19	0.6	1.6	Breast ca.* (pl.ef) MDA- MB-231	0.1	0.4
glioma U251	0.2	0.9	Breast ca.* (pl. ef) T47D	0.1	0.4
glioma SF-295	0.1	0.2	Breast ca. BT- 549	0.0	0.0
Heart	0.3	0.3	Breast ca. MDA-N	0.1	0.6
Skeletal muscle	0.3	0.4	Ovary	3.6	1.3

Bone marrow	3.5	3.0	Ovarian ca. OVCAR-3	0.0	0.1
Thymus	0.3	0.2	Ovarian ca. OVCAR-4	0.0	0.0
Spleen	100.0	100.0	Ovarian ca. OVCAR-5	0.1	0.6
Lymph node	29.3	81.2	Ovarian ca. OVCAR-8	0.2	0.7
Colon (ascending)	0.8	1.0	Ovarian ca. IGROV-1	0.0	0.3
Stomach	1.2	1.5	Ovarian ca. (ascites) SK- OV-3	0.0	0.2
Small intestine	1.6	1.7	Uterus	0.2	0.4
Colon ca. SW480	0.0	0.0	Placenta	1.9	1.6
Colon ca.* SW620 (SW480 met)	0.0	0.1	Prostate	0.7	1.0
Colon ca. HT29	0.0	0.1	Prostate ca.* (bone met) PC-3	0.0	0.0
Colon ca. HCT- 116	0.0	0.0	Testis	23.5	22.1
Colon ca. CaCo-2	0.1	0.1	Melanoma Hs688(A).T	0.0	0.1
Colon ca. HCT-15	0.1	0.7	Melanoma* (met) Hs688(B).T	0.0	0.1
Colon ca. HCC- 2998	0.0	0.3	Melanoma UACC-62	0.0	0.0
Gastric ca. (liver met) NCI-N87	0.1	0.2	Melanoma M14	0.1	0.5
Bladder	1.1	0.2	Melanoma LOX IMVI	0.1	0.5
Trachea	2.4	2.2	Melanoma* (met) SK-MEL- 5	0.0	0.0
Kidney	0.1	0.4	Melanoma SK- MEL-28	0.3	1.3
Kidney (fetal)	1.0	1.3			

Table AK Panel 1.2

Tissue Name	Rel. Exp.(%) Ag812, Run 118348259	Rel. Exp.(%) Ag812, Run 121953945	Tissue Name	Rel. Exp.(%) Ag812, Run 118348259	Rel. Exp.(%) Ag812, Run 121953945
Endothelial cells	0.0	0.0	Renal ca. 786-0	0.0	0.0
Heart (Fetal)	0.3	5.6	Renal ca. A498	0.3	0.1
Pancreas	2.0	0.6	Renal ca. RXF 393	0.0	0.0
Pancreatic ca. CAPAN 2	0.0	0.0	Renal ca. ACHN	0.0	0.0
Adrenal gland	0.3	0.9	Renal ca. UO- 31	0.0	0.0
Thyroid	2.0	0.7	Renal ca. TK- 10	0.0	0.0
Salivary gland	6.3	6.7	Liver	100.0	100.0
Pituitary gland	0.1	0.4	Liver (fetal)	37.9	58.2
Brain (fetal)	0.1	0.0	Liver ca. (hepatoblast) HepG2	0.0	0.0
Brain (whole)	1.2	0.1	Lung	0.4	0.8
Brain (amygdala)	0.0	0.1	Lung (fetal)	2.4	2.5
Brain (cerebellum)	7.6	0.0	Lung ca. (small cell) LX-1	0.0	0.0
Brain (hippocampus)	0.1	0.2	Lung ca. (small cell) NCI-H69	0.1	0.6
Brain (thalamus)	0.0	0.0	Lung ca. (s.cell var.) SHP-77	0.0	0.0
Cerebral Cortex	0.1	0.1	Lung ca. (large cell) NCI-H460	0.0	0.2
Spinal cord	0.0	0.1	Lung ca. (non- sm. cell) A549	0.1	0.2
glio/astro U87- MG	0.0	0.0	Lung ca. (non- s.cell) NCI- H23	0.0	0.1
glio/astro U-118- MG	0.0	0.0	Lung ca. (non- s.cell) HOP-62	0.0	0.0
astrocytoma SW1783	0.0	0.0	Lung ca. (non- s.cl) NCI-H522	0.0	0.0
neuro*; met SK- N-AS	0.0	0.0	Lung ca. (squam.) SW 900	0.0	0.0
astrocytoma SF- 539	0.0	0.1	Lung ca. (squam.) NCI-	0.1	0.2

			H596		
astrocytoma SNB-75	0.0	0.0	Mammary gland	2.9	2.3
glioma SNB-19	0.0	0.1	Breast ca.* (pl.ef) MCF-7	0.0	0.0
glioma U251	0.0	0.1	Breast ca.* (pl.ef) MDA- MB-231	0.0	0.0
glioma SF-295	0.0	0.0	Breast ca.* (pl. ef) T47D	0.1	0.3
Heart	0.8	1.8	Breast ca. BT- 549	0.0	0.0
Skeletal muscle	2.4	1.5	Breast ca. MDA-N	0.0	0.1
Bone marrow	2.7	3.5	Ovary	1.4	4.2
Thymus	0.2	0.3	Ovarian ca. OVCAR-3	2.9	0.0
Spleen	44.8	44.4	Ovarian ca. OVCAR-4	4.1	0.0
Lymph node	39.2	51.8	Ovarian ca. OVCAR-5	0.2	0.3
Colorectal	0.0	0.2	Ovarian ca. OVCAR-8	0.0	0.1
Stomach	1.0	2.9	Ovarian ca. IGROV-1	0.0	0.0
Small intestine	1.2	2.7	Ovarian ca. (ascites) SK- OV-3	0.0	0.0
Colon ca. SW480	0.0	0.0	Uterus	0.2	0.7
Colon ca.* SW620 (SW480 met)	0.0	0.0	Placenta	0.8	0.9
Colon ca. HT29	0.0	0.1	Prostate	0.3	0.5
Colon ca. HCT- 116	0.0	0.0	Prostate ca.* (bone met) PC- 3	0.0	0.0
Colon ca. CaCo- 2	0.0	0.0	Testis	12.2	8.4
CC Well to Mod Diff (ODO3866)	0.1	0.4	Melanoma Hs688(A).T	0.0	0.0
Colon ca. HCC- 2998	0.0	0.0	Melanoma* (met)	0.0	0.1

			Hs688(B).T		
Gastric ca. (liver met) NCI-N87	0.0	0.1	Melanoma UACC-62	0.0	0.0
Bladder	3.7	3.8	Melanoma M14	0.1	0.2
Trachea	1.1	1.9	Melanoma LOX IMVI	0.0	0.0
Kidney	0.1	0.4	Melanoma* (met) SK-MEL-5	0.1	0.0
Kidney (fetal)	0.8	2.1			

Table AL. Panel 1.3D

Tissue Name	Rel. Exp.(%) Ag2742, Run 153641674	Rel. Exp.(%) Ag2743, Run 153658349	Rel. Exp.(%) Ag2744, Run 153670718	Rel. Exp.(%) Ag2745, Run 153664738	Rel. Exp.(%) Ag2746, Run 153675151
Liver adenocarcinoma	0.0	0.0	0.0	0.0	0.0
Pancreas	0.2	0.4	0.3	0.2	0.2
Pancreatic ca. CAPAN 2	0.0	0.0	0.0	0.0	0.0
Adrenal gland	0.2	0.0	0.0	0.4	0.2
Thyroid	0.5	0.6	1.1	1.4	0.6
Salivary gland	1.0	1.0	0.7	0.7	0.1
Pituitary gland	0.0	0.0	0.1	0.0	0.0
Brain (fetal)	0.0	0.0	0.0	0.0	0.0
Brain (whole)	0.0	0.0	0.1	0.0	0.0
Brain (amygdala)	0.0	0.3	0.1	0.0	0.0
Brain (cerebellum)	0.0	0.0	0.0	0.0	0.0
Brain (hippocampus)	0.3	0.0	0.1	0.0	0.0
Brain (substantia nigra)	0.0	0.0	0.0	0.0	0.0
Brain (thalamus)	0.0	0.0	0.0	0.0	0.0
Cerebral Cortex	0.0	0.0	0.0	0.1	0.0
Spinal cord	0.0	0.0	0.0	0.0	0.0
glio/astro U87-MG	0.0	0.0	0.0	0.0	0.0
glio/astro U-118-MG	0.0	0.0	0.0	0.0	0.0

astrocytoma SW1783	0.0	0.0	0.0	0.0	0.0
neuro*; met SK-N-AS	0.0	0.0	0.0	0.0	0.0
astrocytoma SF-539	0.0	0.0	0.0	0.0	0.0
astrocytoma SNB-75	0.0	0.0	0.0	0.0	0.0
glioma SNB-19	0.0	0.0	0.0	0.0	0.0
glioma U251	0.0	0.0	0.0	0.0	0.0
glioma SF-295	0.0	0.0	0.0	0.0	0.0
Heart (Fetal)	1.8	0.7	2.1	2.1	1.5
Heart	0.1	0.2	0.0	0.1	0.2
Skeletal muscle (Fetal)	8.5	6.9	9.3	9.5	6.8
Skeletal muscle	0.0	0.0	0.0	0.1	0.0
Bone marrow	2.6	2.2	3.3	2.4	3.1
Thymus	0.1	0.0	0.1	0.1	0.2
Spleen	100.0	100.0	100.0	100.0	100.0
Lymph node	20.7	17.9	25.5	26.4	32.8
Colorectal	1.6	1.1	0.6	0.7	0.4
Stomach	1.3	0.5	1.2	0.7	0.9
Small intestine	1.3	1.0	1.1	1.1	1.2
Colon ca. SW480	0.0	0.0	0.0	0.0	0.0
Colon ca.* SW620 (SW480 met)	0.0	0.0	0.0	0.0	0.0
Colon ca. HT29	0.0	0.0	0.0	0.0	0.0
Colon ca. HCT-116	0.0	0.0	0.0	0.0	0.0
Colon ca. CaCo-2	0.0	0.0	0.0	0.0	0.0
CC Well to Mod Diff (ODO3866)	0.1	0.1	0.0	0.2	0.1
Colon ca. HCC-2998	0.0	0.0	0.0	0.0	0.0
Gastric ca. (liver met) NCI-N87	0.0	0.0	0.0	0.0	0.1
Bladder	0.3	0.4	0.6	0.6	0.4
Trachea	1.3	0.7	1.4	1.2	1.3
Kidney	0.0	0.0	0.1	0.0	0.0

Kidney (fetal)	2.4	3.4	3.8	2.1	3.0
Renal ca. 786-0	0.0	0.0	0.0	0.0	0.0
Renal ca. A498	0.0	0.0	0.0	0.0	0.0
Renal ca. RXF 393	0.0	0.0	0.0	0.0	0.0
Renal ca. ACHN	0.0	0.0	0.0	0.0	0.0
Renal ca. UO-31	0.0	0.0	0.0	0.0	0.0
Renal ca. TK-10	0.0	0.0	0.0	0.0	0.0
Liver	5.6	8.8	6.1	6.4	10.3
Liver (fetal)	33.4	33.2	33.9	33.4	36.6
Liver ca. (hepatoblast) HepG2	0.0	0.0	0.0	0.0	0.0
Lung	0.6	0.6	0.6	0.7	0.2
Lung (fetal)	2.0	1.9	2.4	1.0	3.1
Lung ca. (small cell) LX-1	0.0	0.0	0.0	0.0	0.0
Lung ca. (small cell) NCI-H69	0.0	0.0	0.0	0.0	0.0
Lung ca. (s.cell var.) SHP-77	0.0	0.0	0.0	0.0	0.0
Lung ca. (large cell) NCI-H460	0.0	0.0	0.0	0.0	0.0
Lung ca. (non-sm. cell) A549	0.0	0.0	0.0	0.0	0.0
Lung ca. (non-s.cell) NCI-H23	0.0	0.0	0.0	0.0	0.0
Lung ca. (non-s.cell) HOP-62	0.0	0.0	0.0	0.0	0.0
Lung ca. (non-s.cl) NCI-H522	0.0	0.0	0.0	0.0	0.0
Lung ca. (squam.) SW 900	0.0	0.0	0.0	0.0	0.0
Lung ca. (squam.) NCI-H596	0.0	0.0	0.0	0.0	0.0
Mammary gland	1.6	1.5	1.1	1.7	1.5
Breast ca.* (pl.ef) MCF-7	0.0	0.0	0.0	0.0	0.0
Breast ca.* (pl.ef) MDA-MB-231	0.0	0.0	0.0	0.0	0.0
Breast ca.* (pl. ef)	0.0	0.0	0.0	0.0	0.0

T47D					
Breast ca. BT-549	0.0	0.0	0.0	0.0	0.0
Breast ca. MDA-N	0.0	0.0	0.0	0.0	0.0
Ovary	5.0	5.4	4.5	6.0	4.6
Ovarian ca. OVCAR-3	0.0	0.0	0.0	0.0	0.0
Ovarian ca. OVCAR-4	0.0	0.0	0.0	0.0	0.0
Ovarian ca. OVCAR-5	0.0	0.0	0.0	0.0	0.0
Ovarian ca. OVCAR-8	0.0	0.0	0.0	0.0	0.0
Ovarian ca. IGROV-1	0.0	0.0	0.0	0.0	0.0
Ovarian ca. (ascites) SK-OV-3	0.0	0.0	0.0	0.0	0.0
Uterus	0.2	0.2	0.5	0.3	0.1
Placenta	0.4	0.0	0.4	0.1	0.2
Prostate	0.2	0.1	0.1	0.1	0.1
Prostate ca.* (bone met) PC-3	0.0	0.0	0.0	0.0	0.0
Testis	7.5	5.9	4.7	6.5	5.6
Melanoma Hs688(A).T	0.0	0.0	0.0	0.0	0.0
Melanoma* (met) Hs688(B).T	0.0	0.0	0.0	0.0	0.0
Melanoma UACC-62	0.0	0.0	0.0	0.0	0.0
Melanoma M14	0.0	0.0	0.0	0.0	0.0
Melanoma LOX IMVI	0.0	0.0	0.0	0.0	0.0
Melanoma* (met) SK-MEL-5	0.0	0.0	0.0	0.0	0.0
Adipose	1.0	1.5	0.6	0.5	1.1

Table AM. Panel 2D

Tissue Name	Rel. Exp.(%) Ag2742, Run 153641758	Rel. Exp.(%) Ag2743, Run 153658357	Rel. Exp.(%) Ag2744, Run 153670751	Rel. Exp.(%) Ag2745, Run 153664739	Rel. Exp.(%) Ag2746, Run 153675220
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Normal Colon	3.2	3.8	4.4	4.8	4.5
CC Well to Mod Diff (ODO3866)	0.1	0.1	0.1	0.0	0.0
CC Margin (ODO3866)	0.7	0.5	0.9	1.2	0.3
CC Gr.2 rectosigmoid (ODO3868)	0.2	0.4	0.2	0.2	0.1
CC Margin (ODO3868)	0.1	0.1	0.0	0.2	0.1
CC Mod Diff (ODO3920)	0.0	0.1	0.1	0.0	0.0
CC Margin (ODO3920)	1.1	2.0	3.1	1.0	1.4
CC Gr.2 ascend colon (ODO3921)	0.2	0.3	0.9	0.5	0.7
CC Margin (ODO3921)	0.7	0.3	0.9	1.0	0.2
CC from Partial Hepatectomy (ODO4309) Mets	7.6	8.4	10.2	9.5	8.8
Liver Margin (ODO4309)	100.0	100.0	100.0	100.0	100.0
Colon mets to lung (OD04451-01)	0.4	0.3	0.3	1.5	0.4
Lung Margin (OD04451-02)	0.2	0.1	0.8	0.2	0.2
Normal Prostate 6546-1	0.4	0.0	0.2	0.1	0.1
Prostate Cancer (OD04410)	0.2	0.2	0.0	0.3	0.0
Prostate Margin (OD04410)	0.0	0.2	0.3	0.0	0.6
Prostate Cancer (OD04720-01)	0.6	0.1	0.2	0.2	0.3
Prostate Margin (OD04720-02)	0.5	0.5	0.6	0.3	0.2
Normal Lung	5.6	5.2	6.3	8.1	5.9
Lung Met to Muscle (ODO4286)	0.0	0.0	0.0	0.0	0.0

Muscle Margin (ODO4286)	0.5	0.0	0.1	0.2	0.0
Lung Malignant Cancer (OD03126)	1.0	1.0	1.3	0.8	1.0
Lung Margin (OD03126)	0.9	1.1	0.9	1.4	1.4
Lung Cancer (OD04404)	1.3	0.8	1.6	1.5	1.4
Lung Margin (OD04404)	2.0	2.5	4.3	3.4	3.2
Lung Cancer (OD04565)	0.2	0.1	0.5	0.0	0.2
Lung Margin (OD04565)	0.3	0.0	0.3	0.4	0.7
Lung Cancer (OD04237-01)	0.4	0.9	1.2	1.5	1.2
Lung Margin (OD04237-02)	5.6	5.4	7.9	6.3	5.6
Ocular Mel Met to Liver (ODO4310)	0.2	0.0	0.0	0.1	0.4
Liver Margin (ODO4310)	52.9	64.6	79.6	81.8	63.3
Melanoma Metastasis	0.0	0.0	0.0	0.1	0.3
Lung Margin (OD04321)	0.2	2.0	0.9	1.5	0.5
Normal Kidney	0.5	0.3	0.3	0.7	0.3
Kidney Ca, Nuclear grade 2 (OD04338)	0.0	0.1	0.0	0.0	0.1
Kidney Margin (OD04338)	0.0	0.2	0.5	0.1	0.3
Kidney Ca Nuclear grade 1/2 (OD04339)	0.0	0.0	0.0	0.0	0.0
Kidney Margin (OD04339)	0.0	0.1	0.1	0.3	0.1
Kidney Ca, Clear cell type (OD04340)	0.0	0.1	0.0	0.0	0.1

Kidney Margin (OD04340)	0.2	0.1	0.8	0.0	0.0
Kidney Ca, Nuclear grade 3 (OD04348)	0.0	0.0	0.2	0.0	0.1
Kidney Margin (OD04348)	0.0	0.1	0.2	0.1	0.1
Kidney Cancer (OD04622-01)	0.2	0.1	0.1	1.2	0.2
Kidney Margin (OD04622-03)	0.0	0.1	0.0	0.0	0.0
Kidney Cancer (OD04450-01)	0.0	0.0	0.0	0.0	0.0
Kidney Margin (OD04450-03)	0.1	0.0	0.1	0.1	0.1
Kidney Cancer 8120607	0.0	0.0	0.0	0.0	0.0
Kidney Margin 8120608	0.1	0.0	0.2	0.0	0.0
Kidney Cancer 8120613	0.3	0.2	0.2	0.1	0.5
Kidney Margin 8120614	0.3	0.1	0.4	0.3	0.0
Kidney Cancer 9010320	0.0	0.1	0.1	0.1	0.2
Kidney Margin 9010321	0.1	0.0	0.0	0.1	0.2
Normal Uterus	0.5	0.1	0.8	0.1	0.5
Uterine Cancer 064011	0.8	0.7	1.3	0.4	0.6
Normal Thyroid	1.8	1.1	1.5	0.9	2.3
Thyroid Cancer	0.0	0.0	0.0	0.0	0.0
Thyroid Cancer A302152	0.5	1.0	1.3	0.6	0.8
Thyroid Margin A302153	2.3	2.4	3.5	3.9	2.4
Normal Breast	9.0	6.8	9.0	9.9	5.5
Breast Cancer	0.1	0.0	0.1	0.0	0.0
Breast Cancer (OD04590-01)	0.3	0.4	0.2	0.7	0.2
Breast Cancer Mets (OD04590-	1.7	2.4	2.5	2.5	1.4

(03)					
Breast Cancer Metastasis	10.7	13.2	22.1	15.6	12.8
Breast Cancer	0.5	0.8	0.8	0.7	0.7
Breast Cancer	4.1	2.5	5.1	3.1	3.6
Breast Cancer 9100266	0.9	0.2	0.2	0.2	0.2
Breast Margin 9100265	0.7	0.4	1.0	0.7	1.2
Breast Cancer A209073	1.2	1.2	1.1	1.9	0.8
Breast Margin A2090734	1.5	1.0	2.1	1.5	0.6
Normal Liver	27.5	27.9	37.4	42.3	27.2
Liver Cancer	0.8	0.5	0.3	0.6	0.5
Liver Cancer 1025	33.7	36.6	36.6	39.0	27.5
Liver Cancer 1026	4.6	3.6	5.7	5.8	5.2
Liver Cancer 6004-T	36.9	38.7	50.3	46.7	38.7
Liver Tissue 6004-N	1.5	1.0	1.3	1.3	1.6
Liver Cancer 6005-T	4.5	3.9	4.2	4.3	2.9
Liver Tissue 6005-N	22.2	24.5	32.8	27.5	28.7
Normal Bladder	5.3	3.4	4.8	4.2	5.5
Bladder Cancer	1.6	1.3	1.5	1.6	1.7
Bladder Cancer	0.9	0.4	1.5	1.0	0.3
Bladder Cancer (OD04718-01)	0.0	0.0	0.0	0.0	0.0
Bladder Normal Adjacent (OD04718-03)	5.2	6.2	7.8	6.0	4.1
Normal Ovary	1.6	3.0	5.4	3.6	3.6
Ovarian Cancer	0.0	0.1	0.1	0.6	0.5
Ovarian Cancer (OD04768-07)	0.0	0.0	0.0	0.1	0.0
Ovary Margin (OD04768-08)	2.3	1.7	3.1	2.4	2.6

Normal Stomach	0.9	0.8	1.7	0.8	0.8
Gastric Cancer 9060358	0.0	0.4	0.8	0.4	0.2
Stomach Margin 9060359	1.2	0.8	1.3	1.0	0.9
Gastric Cancer 9060395	0.1	0.2	0.3	0.5	0.6
Stomach Margin 9060394	0.8	0.6	1.7	0.7	0.6
Gastric Cancer 9060397	0.1	0.1	0.1	0.0	0.0
Stomach Margin 9060396	0.3	0.1	0.6	0.1	0.3
Gastric Cancer 064005	0.7	0.6	0.4	1.1	0.3

Table AN. Panel 4D

Tissue Name	Rel. Exp.(%) Ag2742, Run 153641803	Rel. Exp.(%) Ag2743, Run 153658360	Rel. Exp.(%) Ag2744, Run 153670759	Rel. Exp.(%) Ag2745, Run 153664740	Rel. Exp.(%) Ag2746, Run 153675321	Rel. Exp.(%) Ag812, Run 138175358
Secondary Th1 act	0.0	0.0	0.0	0.0	0.0	0.0
Secondary Th2 act	0.0	0.7	0.0	0.0	0.0	0.0
Secondary Tr1 act	1.7	0.0	1.9	0.0	7.5	2.8
Secondary Th1 rest	0.0	0.0	0.0	0.0	0.0	0.0
Secondary Th2 rest	0.0	0.0	0.0	0.0	0.0	0.0
Secondary Tr1 rest	0.0	0.0	0.0	0.0	0.0	2.8
Primary Th1 act	0.0	0.0	0.0	0.0	0.0	0.0
Primary Th2 act	1.6	0.0	0.0	0.0	0.0	4.8
Primary Tr1 act	0.0	0.0	0.0	0.0	0.0	0.0
Primary Th1 rest	0.0	0.0	0.0	0.0	0.0	0.0
Primary Th2 rest	0.0	0.0	0.0	0.0	0.0	0.0
Primary Tr1 rest	0.0	0.0	0.0	0.0	0.0	0.0
CD45RA CD4 lymphocyte act	0.0	0.0	0.0	0.0	0.0	0.0
CD45RO CD4 lymphocyte act	0.0	0.0	0.0	0.0	0.0	0.0
CD8 lymphocyte act	0.0	0.0	0.0	0.0	0.0	0.0

Secondary CD8 lymphocyte rest	0.0	0.0	0.0	0.0	0.0	0.0
Secondary CD8 lymphocyte act	0.7	0.0	0.0	7.8	0.0	1.8
CD4 lymphocyte none	0.0	0.0	0.0	0.0	0.0	0.0
2ry Th1/Th2/Tr1_anti-CD95 CH11	0.0	0.0	0.0	0.0	0.0	0.0
LAK cells rest	0.0	0.0	0.0	0.0	0.0	0.0
LAK cells IL-2	0.0	0.0	0.0	0.0	0.0	4.7
LAK cells IL-2+IL-12	0.0	0.0	0.0	0.0	1.9	0.0
LAK cells IL-2+IFN gamma	0.0	1.5	3.3	5.0	0.0	3.0
LAK cells IL-2+IL-18	0.0	0.0	2.1	0.0	0.0	0.0
LAK cells PMA/ionomycin	0.0	0.0	0.0	0.0	0.0	0.0
NK Cells IL-2 rest	0.0	0.0	0.0	0.0	0.0	0.0
Two Way MLR 3 day	0.0	0.0	0.0	0.0	0.0	0.0
Two Way MLR 5 day	0.0	0.0	0.0	0.0	0.0	0.0
Two Way MLR 7 day	2.0	0.0	6.4	0.0	0.0	11.3
PBMC rest	0.0	0.0	0.0	0.0	0.0	5.1
PBMC PWM	0.0	2.3	0.0	0.0	0.0	2.7
PBMC PHA-L	0.0	1.5	2.5	0.0	0.0	2.2
Ramos (B cell) none	0.0	0.0	0.0	0.0	0.0	0.0
Ramos (B cell) ionomycin	0.0	0.0	0.0	0.0	0.0	0.0
B lymphocytes PWM	0.0	0.0	0.0	0.0	0.0	2.0
B lymphocytes CD40L and IL-4	0.0	0.0	0.0	0.0	0.0	6.0
EOL-1 dbcAMP	0.0	0.0	0.0	0.0	0.0	0.0
EOL-1 dbcAMP PMA/ionomycin	0.0	0.0	0.0	0.0	0.0	0.0
Dendritic cells	1.4	2.9	0.0	0.0	4.9	0.0

none						
Dendritic cells LPS	0.0	0.0	0.0	0.0	0.0	0.0
Dendritic cells anti-CD40	0.0	0.0	3.3	0.0	0.0	0.0
Monocytes rest	0.0	0.0	0.0	0.0	0.0	0.0
Monocytes LPS	0.0	0.0	0.0	0.0	0.0	0.0
Macrophages rest	0.0	0.0	0.0	0.0	0.0	0.0
Macrophages LPS	0.0	0.0	0.0	2.4	0.0	0.0
HUVEC none	0.0	0.0	0.0	0.0	0.0	0.0
HUVEC starved	0.0	0.0	0.0	0.0	0.0	0.0
HUVEC IL-1beta	0.0	0.0	0.0	0.0	0.0	0.0
HUVEC IFN gamma	3.7	0.0	0.0	0.0	2.7	0.0
HUVEC TNF alpha + IFN gamma	0.0	0.0	0.0	0.0	0.0	0.0
HUVEC TNF alpha + IL4	0.0	0.0	0.0	0.0	0.0	0.0
HUVEC IL-11	1.4	0.0	0.0	0.0	0.0	2.6
Lung Microvascular EC none	1.6	0.0	2.2	0.0	0.0	0.0
Lung Microvascular EC TNFalpha + IL-1beta	3.1	2.9	0.0	0.0	0.0	0.0
Microvascular Dermal EC none	0.0	3.1	5.0	0.0	0.0	12.6
Microvascular Dermal EC TNFalpha + IL-1beta	1.4	1.1	0.0	0.0	1.6	0.0
Bronchial epithelium TNFalpha + IL1beta	0.0	0.0	0.0	0.0	0.0	0.0
Small airway epithelium none	0.0	0.0	0.0	0.0	0.0	0.0
Small airway epithelium TNFalpha + IL-1beta	0.0	0.0	0.0	0.0	0.0	0.0
Coronary artery	0.0	0.0	0.0	0.0	0.0	0.0

SMC rest						
Coronary artery SMC TNFalpha + IL-1beta	0.0	0.0	0.0	0.0	0.0	0.0
Astrocytes rest	0.0	0.0	0.0	0.0	0.0	0.0
Astrocytes TNFalpha + IL- 1beta	0.0	0.0	0.0	0.0	0.0	0.0
KU-812 (Basophil) rest	0.0	0.0	0.0	0.0	0.0	0.0
KU-812 (Basophil) PMA/ionomycin	0.0	0.0	0.0	0.0	0.0	0.0
CCD1106 (Keratinocytes) none	0.0	0.0	0.0	0.0	0.0	0.0
CCD1106 (Keratinocytes) TNFalpha + IL- 1beta	0.0	0.0	0.0	0.0	0.0	
Liver cirrhosis	100.0	100.0	100.0	100.0	100.0	100.0
Lupus kidney	0.0	1.4	0.0	0.0	0.0	0.0
NCI-H292 none	0.0	0.0	0.0	0.0	0.0	0.0
NCI-H292 IL-4	0.0	0.0	0.0	0.0	2.3	0.0
NCI-H292 IL-9	0.0	0.0	0.0	0.0	0.0	0.0
NCI-H292 IL-13	0.0	0.0	0.0	0.0	0.0	0.0
NCI-H292 IFN gamma	0.0	0.0	0.0	0.0	0.0	0.0
HPAEC none	4.8	1.4	0.0	0.0	0.0	3.0
HPAEC TNF alpha + IL-1 beta	0.0	0.0	0.0	0.0	0.0	0.0
Lung fibroblast none	0.0	0.0	0.0	0.0	0.0	0.0
Lung fibroblast TNF alpha + IL-1 beta	0.0	0.0	0.0	0.0	0.0	0.0
Lung fibroblast IL- 4	0.0	0.0	0.0	0.0	0.0	0.0
Lung fibroblast IL- 9	0.0	0.0	0.0	0.0	0.0	0.0
Lung fibroblast IL- 13	0.0	0.0	0.0	0.0	0.0	0.0
Lung fibroblast	0.0	0.0	0.0	0.0	0.0	0.0

IFN gamma						
Dermal fibroblast CCD1070 rest	0.0	0.0	0.0	0.0	0.0	0.0
Dermal fibroblast CCD1070 TNF alpha	0.0	0.0	0.0	0.0	0.0	0.0
Dermal fibroblast CCD1070 IL-1 beta	0.0	0.0	0.0	0.0	0.0	0.0
Dermal fibroblast IFN gamma	0.0	0.0	0.0	0.0	0.0	5.3
Dermal fibroblast IL-4	0.0	0.0	0.0	0.0	0.0	0.0
IBD Colitis 2	1.7	0.0	0.0	0.0	0.0	0.0
IBD Crohn's	4.5	1.6	6.7	6.1	3.3	3.0
Colon	5.5	2.1	23.0	8.3	4.7	11.1
Lung	41.5	26.2	27.7	39.2	37.1	49.7
Thymus	4.2	0.0	4.1	0.0	1.4	20.6
Kidney	4.7	5.2	8.7	5.9	6.3	6.7

Panel 1 Summary: Ag03/Ag068

Two experiments with the same probe and primer set produce results that are in excellent agreement, with highest expression of the AC084364.5 gene in the spleen (CTs=21-25). Overall, this gene appears to be more highly expressed in normal tissue than in cancer cell lines. There are however detectable levels of expression in cell lines derived from melanoma, breast, renal, ovarian, lung, gastric and colon cancers. Thus, the difference in levels of expression of this gene could potentially be used to differentiate between these cancer cell line samples and other samples on this panel and between normal tissues and malignancies from those cancers.

There are also higher levels of expression in lung, and kidney tissue from fetal sources (CTs=25-28) when compared to levels of expression in the adult (CTs=38-31). Thus, expression of this gene could also be used to differentiate between adult and fetal lung and kidney tissue.

Among tissues with metabolic function, this gene is expressed in the liver, pituitary, thyroid, heart, skeletal muscle and adrenal gland. This suggests that the protein encoded by this gene may be involved in the homeostasis of these tissues. Therefore, therapeutic modulation of

the expression or function of this gene product may be effective in the treatment of metabolic disorders, including obesity and diabetes.

This gene is a homolog of Stabilin-1, and is also expressed at moderate levels in all brain regions examined. Because stabilin is involved in angiogenesis, the therapeutic modulation of this gene or its protein product may be of benefit in the treatment of stroke/cerebral ischemia/cerebral infarct.

Panel 1.2 Summary: Ag812

Two experiments with the same probe and primer set show highest expression of the AC084364.5 gene in the liver (CTs=25). Significant expression is also found in other metabolic tissues including fetal and adult heart, skeletal muscle, pancreas, thyroid, pituitary and adrenal gland. The high expression of this gene in the liver suggests that this gene may be involved in the normal homeostasis of that organ. Therapeutic modulation of the expression or function of this gene may be effective in the treatment of disease that involve the liver.

This gene also shows low to moderate expression in the brain. Please see Panel 1 for discussion of potential utility of this gene in the central nervous system.

While this gene shows a greater association for normal tissue, there are significant levels of expression in a cluster of ovarian cancer cell lines. Thus, expression of this gene could be used to differentiate between those samples and other samples on this panel, and between normal and malignant ovarian tissue. Furthermore, therapeutic modulation of the expression or function of this protein may be effective in the treatment of ovarian cancer. Please note that data from a third experiment with the probe and primer set Ag793 is not included, because the controls indicate that the experiment failed.

Panel 1.3D Summary: Ag2742, Ag2743, Ag2744, Ag2745, Ag2746

Multiple experiments with the same probe and primer set produce results that are in excellent agreement, with all experiments showing highest expression of the AC084364.5 gene in the liver (CTs=25). Significant expression is also found in the spleen (CTs=28-29). This result is in concordance with the results from Panel 1.

This gene appears to be expressed at higher levels in the fetal kidney and skeletal muscle (CTs=32-34) than in the comparable adult tissues (CTs=40). Thus, expression of this gene could be used to differentiate between kidney and skeletal muscle tissue from adult and fetal sources. Furthermore, the higher levels of expression of this gene in the fetal tissues suggest that this gene product may be involved in the development of these organs. Thus, therapeutic modulation of the expression or function of these genes may be effective in treating disease of these organs in the adult.

In this panel, this gene appears to exclusively associate with normal tissue samples, a preference that is also observed in panels 1 and 1.2. Thus, absence of expression of this gene may be useful in differentiating between the cancerous cell lines on this panel, and their corresponding normal tissues, specifically cancers of the ovary, breast and colon.

Panel 2D Summary: Ag2742/Ag2743/Ag2744/Ag2745/Ag2746

Multiple experiments with the same probe and primer set show expression of the AC084364.5 gene to be highest and almost exclusive in the liver (CTs=27-29). Furthermore, there is higher expression in liver tissue when compared to colon cancer or melanoma that have metastasized to the liver. This liver specific expression is in concordance with the results from previous panels. The low/undetectable levels of expression in cancer samples are also in agreement with the results observed in the preceding experiments. Thus, the expression profile of this gene suggests that expression of this gene could be used to differentiate between liver tissue and other samples on this panel and as a marker for liver tissue. Furthermore, therapeutic modulation of the expression or function of the protein encoded by this gene could be effective in the treatment of liver cancer or other disease that involve the liver. Additionally, slightly higher expression of this gene is seen in normal bladder, ovary and stomach compared to the adjacent tumor tissue. Hence, expression of this gene might be used as a marker to identify normal tissue from cancerous tissue in these organs. In addition, polypeptide molecules could potentially be used to therapeutically inhibit bladder, ovary and stomach cancer.

Panel 4D Summary: Ag812/Ag2742/Ag2743/Ag2744/Ag2745/Ag2746

The expression of the AC084364.5 gene appears to be highest in samples from cirrhotic liver, (CTs=32-33). Low level expression is also detected in samples derived from normal lung.

The presence of this gene in liver cirrhosis (a component of which involves liver inflammation and fibrosis) suggests that therapeutic agents involving this gene may be useful in reducing or inhibiting the inflammation associated with fibrotic and other inflammatory diseases.

5 NOV2a and NOV2b (CG50646-04/cg142106342 and CG50646-05: polydom protein)

Expression of gene CG50646-04 and variant CG50646-05 was assessed using the primer-probe set Ag768, described in Table BA. Results of the RTQ-PCR runs are shown in Tables BB and BC.

Table BA. Probe Name Ag768

Primers	Sequences	Length	Start Position
Forward	5'-gggctataagtcagtcggaagt-3' (SEQ ID NO:142)	22	6772
Probe	TET-5'-cctgtatttgtctgccaaagccaatcg-3'-TAMRA (SEQ ID NO:143)	26	6794
Reverse	5'-acagtcgagaggaacacacatc-3' (SEQ ID NO:144)	22	6844

10

Table BB. Panel 1.2

Tissue Name	Rel. Exp.(%) Ag768, Run 116422776	Tissue Name	Rel. Exp.(%) Ag768, Run 116422776
Endothelial cells	0.0	Renal ca. 786-0	0.0
Heart (Fetal)	0.0	Renal ca. A498	0.0
Pancreas	0.0	Renal ca. RXF 393	0.0
Pancreatic ca. CAPAN 2	0.0	Renal ca. ACHN	0.0
Adrenal gland	0.1	Renal ca. UO-31	0.0
Thyroid	0.0	Renal ca. TK-10	0.0
Salivary gland	0.0	Liver	0.0
Pituitary gland	0.0	Liver (fetal)	0.0
Brain (fetal)	0.0	Liver ca. (hepatoblast) HepG2	0.0
Brain (whole)	0.0	Lung	0.6
Brain (amygdala)	0.0	Lung (fetal)	0.0
Brain (cerebellum)	0.0	Lung ca. (small cell) LX-1	0.0
Brain (hippocampus)	0.0	Lung ca. (small cell)	0.0

		NCI-H69	
Brain (thalamus)	0.0	Lung ca. (s.cell var.) SHP-77	0.0
Cerebral Cortex	0.0	Lung ca. (large cell) NCI-H460	0.0
Spinal cord	0.0	Lung ca. (non-sm. cell) A549	0.0
glio/astro U87-MG	0.0	Lung ca. (non-s.cell) NCI-H23	0.0
glio/astro U-118-MG	0.0	Lung ca. (non-s.cell) HOP-62	0.0
astrocytoma SW1783	0.0	Lung ca. (non-s.cl) NCI-H522	0.0
neuro*; met SK-N-AS	0.0	Lung ca. (squam.) SW 900	0.0
astrocytoma SF-539	0.0	Lung ca. (squam.) NCI-H596	0.0
astrocytoma SNB-75	0.0	Mammary gland	4.4
glioma SNB-19	0.0	Breast ca.* (pl.ef) MCF-7	0.0
glioma U251	0.0	Breast ca.* (pl.ef) MDA-MB-231	0.0
glioma SF-295	0.0	Breast ca.* (pl. ef) T47D	0.0
Heart	0.1	Breast ca. BT-549	0.0
Skeletal muscle	0.2	Breast ca. MDA-N	0.0
Bone marrow	0.0	Ovary	0.0
Thymus	0.0	Ovarian ca. OVCAR-3	0.0
Spleen	0.0	Ovarian ca. OVCAR-4	0.0
Lymph node	0.7	Ovarian ca. OVCAR-5	0.0
Colorectal	0.0	Ovarian ca. OVCAR-8	0.0
Stomach	0.0	Ovarian ca. IGROV-1	0.0
Small intestine	0.8	Ovarian ca. (ascites) SK-OV-3	0.0
Colon ca. SW480	0.0	Uterus	0.2
Colon ca.* SW620 (SW480 met)	0.0	Placenta	100.0
Colon ca. HT29	0.0	Prostate	0.0
Colon ca. HCT-116	0.0	Prostate ca.* (bone met) PC-3	0.0
Colon ca. CaCo-2	0.0	Testis	0.0

CC Well to Mod Diff (ODO3866)	0.0	Melanoma Hs688(A).T	0.0
Colon ca. HCC-2998	0.0	Melanoma* (met) Hs688(B).T	0.0
Gastric ca. (liver met) NCI-N87	0.0	Melanoma UACC-62	0.0
Bladder	0.0	Melanoma M14	0.0
Trachea	0.0	Melanoma LOX IMVI	0.0
Kidney	0.0	Melanoma* (met) SK- MEL-5	0.0
Kidney (fetal)	0.0		

Table BC. Panel 4D

Tissue Name	Rel. Exp.(%) Ag768, Run 138175130	Tissue Name	Rel. Exp.(%) Ag768, Run 138175130
Secondary Th1 act	0.0	HUVEC IL-1beta	0.2
Secondary Th2 act	0.1	HUVEC IFN gamma	0.3
Secondary Tr1 act	0.0	HUVEC TNF alpha + IFN gamma	0.1
Secondary Th1 rest	0.1	HUVEC TNF alpha + IL4	0.1
Secondary Th2 rest	0.1	HUVEC IL-11	0.1
Secondary Tr1 rest	0.2	Lung Microvascular EC none	0.0
Primary Th1 act	0.0	Lung Microvascular EC TNFalpha + IL-1beta	0.0
Primary Th2 act	0.0	Microvascular Dermal EC none	0.1
Primary Tr1 act	0.0	Microvascular Dermal EC TNFalpha + IL-1beta	0.2
Primary Th1 rest	0.2	Bronchial epithelium TNFalpha + IL1beta	0.2
Primary Th2 rest	0.0	Small airway epithelium none	2.3
Primary Tr1 rest	0.0	Small airway epithelium TNFalpha + IL-1beta	1.3
CD45RA CD4 lymphocyte act	6.4	Coronary artery SMC rest	15.1
CD45RO CD4 lymphocyte act	0.1	Coronary artery SMC TNFalpha + IL-1beta	8.2
CD8 lymphocyte act	0.0	Astrocytes rest	1.8
Secondary CD8	0.1	Astrocytes TNFalpha + IL-	2.4

lymphocyte rest		1beta	
Secondary CD8 lymphocyte act	0.1	KU-812 (Basophil) rest	0.0
CD4 lymphocyte none	0.0	KU-812 (Basophil) PMA/ionomycin	0.0
2ry Th1/Th2/Tr1_anti-CD95 CH11	0.0	CCD1106 (Keratinocytes) none	0.4
LAK cells rest	0.2	93580_CCD1106 (Keratinocytes)_TNFa and IFNg	1.4
LAK cells IL-2	0.0	Liver cirrhosis	10.6
LAK cells IL-2+IL-12	0.1	Lupus kidney	7.0
LAK cells IL-2+IFN gamma	0.3	NCI-H292 none	24.1
LAK cells IL-2+ IL-18	0.2	NCI-H292 IL-4	21.6
LAK cells PMA/ionomycin	3.5	NCI-H292 IL-9	30.4
NK Cells IL-2 rest	0.0	NCI-H292 IL-13	15.3
Two Way MLR 3 day	0.0	NCI-H292 IFN gamma	14.6
Two Way MLR 5 day	0.0	HPAEC none	0.4
Two Way MLR 7 day	0.0	HPAEC TNF alpha + IL-1 beta	0.0
PBMC rest	0.0	Lung fibroblast none	31.0
PBMC PWM	2.5	Lung fibroblast TNF alpha + IL-1 beta	7.7
PBMC PHA-L	0.3	Lung fibroblast IL-4	55.5
Ramos (B cell) none	0.0	Lung fibroblast IL-9	37.4
Ramos (B cell) ionomycin	0.1	Lung fibroblast IL-13	86.5
B lymphocytes PWM	0.1	Lung fibroblast IFN gamma	100.0
B lymphocytes CD40L and IL-4	0.0	Dermal fibroblast CCD1070 rest	28.9
EOL-1 dbcAMP	0.0	Dermal fibroblast CCD1070 TNF alpha	23.7
EOL-1 dbcAMP PMA/ionomycin	0.0	Dermal fibroblast CCD1070 IL-1 beta	20.2
Dendritic cells none	0.0	Dermal fibroblast IFN gamma	22.5
Dendritic cells LPS	0.2	Dermal fibroblast IL-4	47.0
Dendritic cells anti-CD40	0.1	IBD Colitis 2	0.5
Monocytes rest	0.1	IBD Crohn's	2.0

Monocytes LPS	3.1	Colon	9.2
Macrophages rest	0.1	Lung	20.3
Macrophages LPS	3.3	Thymus	13.0
HUVEC none	0.0	Kidney	6.4
HUVEC starved	0.2		

Panel 1.2 Summary: Ag768

Highest expression of the CG50646-04 (NOV2a) gene is seen in placenta (CT=21). This gene encodes a polydom-like protein and is also highly expressed in mammary gland, skeletal muscle. This gene may be involved in cellular adhesion (ref. 1). Thus, expression of this gene may be used to differentiate between placental tissues and other tissues on this panel. Modulation of this gene or its protein product may be useful in reproductive and skeletal muscle physiology.

This gene is more highly expressed in fetal kidney (CT=33) than in adult kidney (CT=40). Conversely, this gene is more highly expressed in adult lung and liver (CTs=28-32) than in fetal lung and liver (CTs=38-40). Thus, expression of this gene could be used to differentiate between the adult and fetal sources of these tissues.

References:

Gilges D, Vinit MA, Callebaut I, Coulombel L, Cacheux V, Romeo PH, Vigon I.

Polydom: a secreted protein with pentraxin, complement control protein, epidermal growth factor and von Willebrand factor A domains. *Biochem J* 2000 Nov 15;352 Pt 1:49-59

To identify extracellular proteins with epidermal growth factor (EGF) domains that are potentially involved in the control of haemopoiesis, we performed degenerate reverse-transcriptase-mediated PCR on the murine bone-marrow stromal cell line MS-5 and isolated a new partial cDNA encoding EGF-like domains related to those in the Notch proteins. Cloning and sequencing of the full-length cDNA showed that it encoded a new extracellular multi-domain protein that we named polydom. This 387 kDa mosaic protein contained a signal peptide followed by a new association of eight different protein domains, including a pentraxin domain and a von Willebrand factor type A domain, ten EGF domains, and 34 complement control protein modules. The human polydom mRNA is strongly expressed in placenta, its expression in the other tissues

being weak or undetectable. The particular multidomain structure of the encoded protein suggests an important biological role in cellular adhesion and/or in the immune system.

PMID: 11062057

Panel 4D Summary: Ag768

5 Highest expression of the CG50646-04 gene is seen in lung fibroblasts stimulated with IFN-gamma (CT=27.4). Significant expression is seen in many samples derived from the lung including lung fibroblasts stimulated with different cytokines, the pulmonary mucoepidermoid cell line H292 stimulated with the same cytokines, and normal lung tissue. The expression of this gene in lung cells and lung tissue suggests that this gene may be involved in normal homeostasis
10 of the lung, as well as pathological and inflammatory lung disorders, including chronic obstructive pulmonary disease, asthma, allergy and emphysema.

Significant levels of expression of this gene in dermal fibroblasts suggests that this gene may be involved in skin disorders, including psoriasis.

Moderate to low expression of this gene is also seen in many other cells with important
15 immune function, including stimulated macrophages and monocytes, coronary artery smooth muscle cells, stimulated peripheral blood mononuclear cells, lymphocyte activated killer cells (LAK), astrocytes, activated CD45RA cells, and normal colon, thymus and kidney. This widespread expression suggests that this protein encoded by this gene may be involved in other inflammatory and autoimmune conditions, including inflammatory bowel disease, rheumatoid
20 arthritis and osteoarthritis.

NOV3a and NOV3b (CG50273-01 and CG50273-02/152792120 :Novel transmembrane protein)

Expression of gene CG50273-01 and variant CG50273-02 was assessed using the primer-
25 probe set Ag2556, described in Table CA. Results of the RTQ-PCR runs are shown in Tables CB, CC, CD, CE, CF and CG.

Table CA. Probe Name Ag2556

Primers	Sequences	Length	Start Position
Forward	5'-gaggacagctttgatttcattg-3' (SEQ ID NO:145)	22	526
Probe	TET-5'-tggatttgatccatttctctctacca-3'-TAMRA (SEQ ID NO:146)	27	549
Reverse	5'-aagagactggatggcttttcat-3' (SEQ ID NO:147)	22	581

Table CB. CNS_neurodegeneration_v1.0

Tissue Name	Rel. Exp.(%) Ag2556, Run 206974724	Tissue Name	Rel. Exp.(%) Ag2556, Run 206974724
AD 1 Hippo	22.4	Control (Path) 3 Temporal Ctx	6.9
AD 2 Hippo	100.0	Control (Path) 4 Temporal Ctx	21.8
AD 3 Hippo	3.7	AD 1 Occipital Ctx	6.1
AD 4 Hippo	33.0	AD 2 Occipital Ctx (Missing)	0.0
AD 5 Hippo	21.9	AD 3 Occipital Ctx	2.1
AD 6 Hippo	71.2	AD 4 Occipital Ctx	21.9
Control 2 Hippo	55.5	AD 5 Occipital Ctx	18.2
Control 4 Hippo	55.5	AD 5 Occipital Ctx	3.0
Control (Path) 3 Hippo	14.4	Control 1 Occipital Ctx	2.3
AD 1 Temporal Ctx	14.1	Control 2 Occipital Ctx	19.5
AD 2 Temporal Ctx	57.4	Control 3 Occipital Ctx	9.3
AD 3 Temporal Ctx	5.3	Control 4 Occipital Ctx	13.6
AD 4 Temporal Ctx	39.5	Control (Path) 1 Occipital Ctx	41.5
AD 5 Inf Temporal Ctx	42.0	Control (Path) 2 Occipital Ctx	6.1
AD 5 Sup Temporal Ctx	66.0	Control (Path) 3 Occipital Ctx	1.8
AD 6 Inf Temporal Ctx	26.1	Control (Path) 4 Occipital Ctx	9.0
AD 6 Sup Temporal Ctx	14.1	Control 1 Parietal Ctx	12.0
Control 1 Temporal Ctx	18.8	Control 2 Parietal Ctx	41.5

Control 2 Temporal Ctx	29.3	Control 3 Parietal Ctx	12.6
Control 3 Temporal Ctx	14.0	Control (Path) 1 Parietal Ctx	27.9
Control 3 Temporal Ctx	26.1	Control (Path) 2 Parietal Ctx	16.6
Control (Path) 1 Temporal Ctx	43.8	Control (Path) 3 Parietal Ctx	2.9
Control (Path) 2 Temporal Ctx	42.0	Control (Path) 4 Parietal Ctx	17.6

Table CC. Panel 1.3D

Tissue Name	Rel. Exp.(%) Ag2556, Run 162292610	Tissue Name	Rel. Exp.(%) Ag2556, Run 162292610
Liver adenocarcinoma	0.0	Kidney (fetal)	5.6
Pancreas	0.0	Renal ca. 786-0	6.3
Pancreatic ca. CAPAN 2	0.0	Renal ca. A498	0.5
Adrenal gland	0.7	Renal ca. RXF 393	2.0
Thyroid	0.4	Renal ca. ACHN	3.3
Salivary gland	0.6	Renal ca. UO-31	0.9
Pituitary gland	2.8	Renal ca. TK-10	24.3
Brain (fetal)	3.7	Liver	0.0
Brain (whole)	22.7	Liver (fetal)	0.0
Brain (amygdala)	59.9	Liver ca. (hepatoblast) HepG2	0.0
Brain (cerebellum)	39.0	Lung	0.0
Brain (hippocampus)	83.5	Lung (fetal)	0.0
Brain (substantia nigra)	30.8	Lung ca. (small cell) LX-1	0.0
Brain (thalamus)	40.3	Lung ca. (small cell) NCI-H69	0.0
Cerebral Cortex	55.9	Lung ca. (s.cell var.) SHP-77	0.0
Spinal cord	72.2	Lung ca. (large cell) NCI-H460	0.0
glio/astro U87-MG	0.0	Lung ca. (non-sm. cell) A549	0.0
glio/astro U-118-MG	0.0	Lung ca. (non-s.cell) NCI-H23	0.0

astrocytoma SW1783	0.0	Lung ca. (non-s.cell) HOP-62	0.0
neuro*; met SK-N-AS	0.0	Lung ca. (non-s.cl) NCI-H522	0.0
astrocytoma SF-539	0.0	Lung ca. (squam.) SW 900	0.5
astrocytoma SNB-75	0.0	Lung ca. (squam.) NCI-H596	0.0
glioma SNB-19	0.4	Mammary gland	0.0
glioma U251	0.0	Breast ca.* (pl.ef) MCF-7	0.0
glioma SF-295	0.0	Breast ca.* (pl.ef) MDA-MB-231	0.0
Heart (Fetal)	4.5	Breast ca.* (pl. ef) T47D	0.0
Heart	0.0	Breast ca. BT-549	0.0
Skeletal muscle (Fetal)	100.0	Breast ca. MDA-N	0.0
Skeletal muscle	0.0	Ovary	0.4
Bone marrow	0.0	Ovarian ca. OVCAR- 3	0.0
Thymus	5.2	Ovarian ca. OVCAR- 4	0.7
Spleen	0.0	Ovarian ca. OVCAR- 5	2.0
Lymph node	0.0	Ovarian ca. OVCAR- 8	0.9
Colorectal	2.7	Ovarian ca. IGROV-1	0.0
Stomach	0.0	Ovarian ca. (ascites) SK-OV-3	20.7
Small intestine	0.8	Uterus	0.5
Colon ca. SW480	0.0	Placenta	11.0
Colon ca.* SW620 (SW480 met)	0.0	Prostate	0.0
Colon ca. HT29	0.0	Prostate ca.* (bone met) PC-3	0.0
Colon ca. HCT-116	0.0	Testis	5.6
Colon ca. CaCo-2	7.3	Melanoma Hs688(A).T	0.0
CC Well to Mod Diff (ODO3866)	0.5	Melanoma* (met) Hs688(B).T	0.0
Colon ca. HCC-2998	0.0	Melanoma UACC-62	0.0

Gastric ca. (liver met) NCI-N87	0.0	Melanoma M14	0.0
Bladder	0.0	Melanoma LOX IMVI	0.0
Trachea	1.1	Melanoma* (met) SK-MEL-5	0.0
Kidney	20.4	Adipose	0.8

Table CD. Panel 2D

Tissue Name	Rel. Exp.(%) Ag2556, Run 161921170	Tissue Name	Rel. Exp.(%) Ag2556, Run 161921170
Normal Colon	1.0	Kidney Margin 8120608	30.6
CC Well to Mod Diff (ODO3866)	0.0	Kidney Cancer 8120613	0.3
CC Margin (ODO3866)	0.1	Kidney Margin 8120614	4.1
CC Gr.2 rectosigmoid (ODO3868)	0.0	Kidney Cancer 9010320	3.7
CC Margin (ODO3868)	0.1	Kidney Margin 9010321	100.0
CC Mod Diff (ODO3920)	0.3	Normal Uterus	0.0
CC Margin (ODO3920)	0.0	Uterine Cancer 064011	0.0
CC Gr.2 ascend colon (ODO3921)	0.3	Normal Thyroid	0.8
CC Margin (ODO3921)	0.0	Thyroid Cancer	0.4
CC from Partial Hepatectomy (ODO4309) Mets	0.3	Thyroid Cancer A302152	1.5
Liver Margin (ODO4309)	0.0	Thyroid Margin A302153	1.4
Colon mets to lung (OD04451-01)	0.0	Normal Breast	0.0
Lung Margin (OD04451- 02)	0.1	Breast Cancer	0.0
Normal Prostate 6546-1	0.2	Breast Cancer (OD04590-01)	0.0
Prostate Cancer (OD04410)	0.1	Breast Cancer Mets (OD04590-03)	0.0
Prostate Margin	0.3	Breast Cancer	0.0

(OD04410)		Metastasis	
Prostate Cancer (OD04720-01)	0.3	Breast Cancer	0.2
Prostate Margin (OD04720-02)	0.0	Breast Cancer	0.1
Normal Lung	0.1	Breast Cancer 9100266	0.0
Lung Met to Muscle (ODO4286)	0.0	Breast Margin 9100265	0.1
Muscle Margin (ODO4286)	0.0	Breast Cancer A209073	0.0
Lung Malignant Cancer (OD03126)	1.0	Breast Margin A2090734	0.0
Lung Margin (OD03126)	0.1	Normal Liver	0.0
Lung Cancer (OD04404)	0.0	Liver Cancer	0.0
Lung Margin (OD04404)	0.0	Liver Cancer 1025	0.0
Lung Cancer (OD04565)	0.2	Liver Cancer 1026	0.0
Lung Margin (OD04565)	0.0	Liver Cancer 6004-T	0.0
Lung Cancer (OD04237- 01)	0.1	Liver Tissue 6004-N	0.0
Lung Margin (OD04237- 02)	0.1	Liver Cancer 6005-T	0.0
Ocular Mel Met to Liver (ODO4310)	1.0	Liver Tissue 6005-N	0.0
Liver Margin (ODO4310)	0.0	Normal Bladder	0.0
Melanoma Metastasis	0.3	Bladder Cancer	0.0
Lung Margin (OD04321)	0.0	Bladder Cancer	0.0
Normal Kidney	2.4	Bladder Cancer (OD04718-01)	0.9
Kidney Ca, Nuclear grade 2 (OD04338)	15.1	Bladder Normal Adjacent (OD04718- 03)	0.0
Kidney Margin (OD04338)	16.0	Normal Ovary	0.0
Kidney Ca Nuclear grade 1/2 (OD04339)	3.7	Ovarian Cancer	0.1
Kidney Margin (OD04339)	15.9	Ovarian Cancer (OD04768-07)	0.2
Kidney Ca, Clear cell type (OD04340)	1.6	Ovary Margin (OD04768-08)	0.1
Kidney Margin (OD04340)	3.3	Normal Stomach	0.3

Kidney Ca, Nuclear grade 3 (OD04348)	0.1	Gastric Cancer 9060358	0.2
Kidney Margin (OD04348)	20.3	Stomach Margin 9060359	0.0
Kidney Cancer (OD04622-01)	8.8	Gastric Cancer 9060395	0.2
Kidney Margin (OD04622-03)	6.0	Stomach Margin 9060394	0.1
Kidney Cancer (OD04450-01)	1.9	Gastric Cancer 9060397	0.3
Kidney Margin (OD04450-03)	1.9	Stomach Margin 9060396	0.0
Kidney Cancer 8120607	0.2	Gastric Cancer 064005	0.3

Table CE. Panel 3D

Tissue Name	Rel. Exp.(%) Ag2556, Run 164827571	Tissue Name	Rel. Exp.(%) Ag2556, Run 164827571
Daoy- Medulloblastoma	1.8	Ca Ski- Cervical epidermoid carcinoma (metastasis)	0.0
TE671- Medulloblastoma	100.0	ES-2- Ovarian clear cell carcinoma	0.0
D283 Med- Medulloblastoma	0.0	Ramos- Stimulated with PMA/ionomycin 6h	0.0
PFSK-1- Primitive Neuroectodermal	0.0	Ramos- Stimulated with PMA/ionomycin 14h	0.0
XF-498- CNS	0.5	MEG-01- Chronic myelogenous leukemia (megokaryoblast)	0.0
SNB-78- Glioma	0.4	Raji- Burkitt's lymphoma	0.0
SF-268- Glioblastoma	0.0	Daudi- Burkitt's lymphoma	0.0
T98G- Glioblastoma	0.0	U266- B-cell plasmacytoma	0.0
SK-N-SH- Neuroblastoma (metastasis)	0.0	CA46- Burkitt's lymphoma	0.0
SF-295- Glioblastoma	0.0	RL- non-Hodgkin's B-cell lymphoma	0.0
Cerebellum	30.8	JM1- pre-B-cell lymphoma	0.3
Cerebellum	49.3	Jurkat- T cell leukemia	0.0
NCI-H292- Mucoepidermoid lung carcinoma	0.0	TF-1- Erythroleukemia	0.0

DMS-114- Small cell lung cancer	1.1	HUT 78- T-cell lymphoma	0.3
DMS-79- Small cell lung cancer	32.5	U937- Histiocytic lymphoma	0.0
NCI-H146- Small cell lung cancer	0.0	KU-812- Myelogenous leukemia	0.0
NCI-H526- Small cell lung cancer	0.0	769-P- Clear cell renal carcinoma	2.4
NCI-N417- Small cell lung cancer	0.0	Caki-2- Clear cell renal carcinoma	0.6
NCI-H82- Small cell lung cancer	0.0	SW 839- Clear cell renal carcinoma	0.0
NCI-H157- Squamous cell lung cancer (metastasis)	0.0	G401- Wilms' tumor	9.5
NCI-H1155- Large cell lung cancer	0.0	Hs766T- Pancreatic carcinoma (LN metastasis)	0.0
NCI-H1299- Large cell lung cancer	0.0	CAPAN-1- Pancreatic adenocarcinoma (liver metastasis)	0.0
NCI-H727- Lung carcinoid	4.1	SU86.86- Pancreatic carcinoma (liver metastasis)	0.6
NCI-UMC-11- Lung carcinoid	0.0	BxPC-3- Pancreatic adenocarcinoma	0.0
LX-1- Small cell lung cancer	0.4	HPAC- Pancreatic adenocarcinoma	1.0
Colo-205- Colon cancer	0.0	MIA PaCa-2- Pancreatic carcinoma	1.9
KM12- Colon cancer	0.0	CFPAC-1- Pancreatic ductal adenocarcinoma	0.0
KM20L2- Colon cancer	0.0	PANC-1- Pancreatic epithelioid ductal carcinoma	7.7
NCI-H716- Colon cancer	0.0	T24- Bladder carcinoma (transitional cell)	0.3
SW-48- Colon adenocarcinoma	0.0	5637- Bladder carcinoma	0.0
SW1116- Colon adenocarcinoma	0.0	HT-1197- Bladder carcinoma	3.7
LS 174T- Colon adenocarcinoma	0.0	UM-UC-3- Bladder carcinoma (transitional cell)	0.0
SW-948- Colon adenocarcinoma	0.0	A204- Rhabdomyosarcoma	0.0
SW-480- Colon	0.0	HT-1080- Fibrosarcoma	0.0

adenocarcinoma			
NCI-SNU-5- Gastric carcinoma	0.0	MG-63- Osteosarcoma	0.4
KATO III- Gastric carcinoma	0.0	SK-LMS-1- Leiomyosarcoma (vulva)	0.0
NCI-SNU-16- Gastric carcinoma	0.0	SJRH30- Rhabdomyosarcoma (met to bone marrow)	3.0
NCI-SNU-1- Gastric carcinoma	0.0	A431- Epidermoid carcinoma	0.0
RF-1- Gastric adenocarcinoma	0.0	WM266-4- Melanoma	0.0
RF-48- Gastric adenocarcinoma	0.0	DU 145- Prostate carcinoma (brain metastasis)	0.0
MKN-45- Gastric carcinoma	0.0	MDA-MB-468- Breast adenocarcinoma	0.0
NCI-N87- Gastric carcinoma	0.0	SCC-4- Squamous cell carcinoma of tongue	0.0
OVCAR-5- Ovarian carcinoma	0.0	SCC-9- Squamous cell carcinoma of tongue	0.0
RL95-2- Uterine carcinoma	0.0	SCC-15- Squamous cell carcinoma of tongue	0.0
HelaS3- Cervical adenocarcinoma	0.0	CAL 27- Squamous cell carcinoma of tongue	0.0

Table CF. Panel 4D

Tissue Name	Rel. Exp.(%) Ag2556, Run 164035630	Tissue Name	Rel. Exp.(%) Ag2556, Run 164035630
Secondary Th1 act	0.0	HUVEC IL-1beta	0.0
Secondary Th2 act	0.0	HUVEC IFN gamma	0.0
Secondary Tr1 act	0.0	HUVEC TNF alpha + IFN gamma	0.0
Secondary Th1 rest	0.0	HUVEC TNF alpha + IL4	0.0
Secondary Th2 rest	0.0	HUVEC IL-11	0.0
Secondary Tr1 rest	0.0	Lung Microvascular EC none	0.0
Primary Th1 act	0.0	Lung Microvascular EC TNFalpha + IL-1beta	0.0
Primary Th2 act	0.0	Microvascular Dermal EC none	0.0
Primary Tr1 act	0.0	Microvascular Dermal EC	0.0

		TNFalpha + IL-1beta	
Primary Th1 rest	0.0	Bronchial epithelium TNFalpha + IL1beta	0.7
Primary Th2 rest	0.0	Small airway epithelium none	1.4
Primary Tr1 rest	0.0	Small airway epithelium TNFalpha + IL-1beta	5.0
CD45RA CD4 lymphocyte act	0.0	Coronary artery SMC rest	0.0
CD45RO CD4 lymphocyte act	0.0	Coronary artery SMC TNFalpha + IL-1beta	0.0
CD8 lymphocyte act	0.0	Astrocytes rest	0.0
Secondary CD8 lymphocyte rest	0.0	Astrocytes TNFalpha + IL- 1beta	0.0
Secondary CD8 lymphocyte act	0.0	KU-812 (Basophil) rest	0.0
CD4 lymphocyte none	0.0	KU-812 (Basophil) PMA/ionomycin	0.0
2ry Th1/Th2/Tr1_anti- CD95 CH11	0.0	CCD1106 (Keratinocytes) none	0.0
LAK cells rest	0.0	CCD1106 (Keratinocytes) TNFalpha + IL-1beta	0.0
LAK cells IL-2	0.0	Liver cirrhosis	0.0
LAK cells IL-2+IL-12	0.0	Lupus kidney	3.2
LAK cells IL-2+IFN gamma	0.0	NCI-H292 none	0.0
LAK cells IL-2+ IL-18	0.0	NCI-H292 IL-4	0.0
LAK cells PMA/ionomycin	0.0	NCI-H292 IL-9	0.0
NK Cells IL-2 rest	0.0	NCI-H292 IL-13	0.0
Two Way MLR 3 day	0.0	NCI-H292 IFN gamma	0.0
Two Way MLR 5 day	0.0	HPAEC none	0.0
Two Way MLR 7 day	0.0	HPAEC TNF alpha + IL-1 beta	0.0
PBMC rest	0.0	Lung fibroblast none	0.0
PBMC PWM	0.0	Lung fibroblast TNF alpha + IL-1 beta	0.0
PBMC PHA-L	0.0	Lung fibroblast IL-4	0.0
Ramos (B cell) none	0.0	Lung fibroblast IL-9	0.0
Ramos (B cell) ionomycin	0.0	Lung fibroblast IL-13	0.0

B lymphocytes PWM	0.0	Lung fibroblast IFN gamma	0.0
B lymphocytes CD40L and IL-4	0.0	Dermal fibroblast CCD1070 rest	0.0
EOL-1 dbcAMP	0.0	Dermal fibroblast CCD1070 TNF alpha	0.0
EOL-1 dbcAMP PMA/ionomycin	0.0	Dermal fibroblast CCD1070 IL-1 beta	0.0
Dendritic cells none	0.0	Dermal fibroblast IFN gamma	0.0
Dendritic cells LPS	0.0	Dermal fibroblast IL-4	0.0
Dendritic cells anti-CD40	0.0	IBD Colitis 2	0.0
Monocytes rest	0.0	IBD Crohn's	0.0
Monocytes LPS	0.0	Colon	5.2
Macrophages rest	0.0	Lung	1.3
Macrophages LPS	0.0	Thymus	100.0
HUVEC none	0.0	Kidney	12.9
HUVEC starved	0.0		

Table CG. Panel CNS_1

Tissue Name	Rel. Exp.(%) Ag2556, Run 171656437	Tissue Name	Rel. Exp.(%) Ag2556, Run 171656437
BA4 Control	15.2	BA17 PSP	8.5
BA4 Control2	21.9	BA17 PSP2	0.0
BA4 Alzheimer's2	4.4	Sub Nigra Control	66.9
BA4 Parkinson's	34.9	Sub Nigra Control2	41.2
BA4 Parkinson's2	12.9	Sub Nigra Alzheimer's2	33.4
BA4 Huntington's	28.9	Sub Nigra Parkinson's2	71.7
BA4 Huntington's2	16.5	Sub Nigra Huntington's	92.7
BA4 PSP	7.0	Sub Nigra Huntington's2	12.9
BA4 PSP2	18.3	Sub Nigra PSP2	20.6
BA4 Depression	12.2	Sub Nigra Depression	10.2
BA4 Depression2	3.5	Sub Nigra Depression2	5.9
BA7 Control	5.8	Glob Palladus	40.9

		Control	
BA7 Control2	17.0	Glob Palladus Control2	34.6
BA7 Alzheimer's2	10.9	Glob Palladus Alzheimer's	42.9
BA7 Parkinson's	30.4	Glob Palladus Alzheimer's2	14.8
BA7 Parkinson's2	8.2	Glob Palladus Parkinson's	100.0
BA7 Huntington's	19.8	Glob Palladus Parkinson's2	20.6
BA7 Huntington's2	32.8	Glob Palladus PSP	16.5
BA7 PSP	16.3	Glob Palladus PSP2	23.0
BA7 PSP2	12.1	Glob Palladus Depression	13.4
BA7 Depression	4.9	Temp Pole Control	10.8
BA9 Control	17.0	Temp Pole Control2	58.6
BA9 Control2	54.0	Temp Pole Alzheimer's	27.5
BA9 Alzheimer's	10.3	Temp Pole Alzheimer's2	13.4
BA9 Alzheimer's2	26.8	Temp Pole Parkinson's	34.4
BA9 Parkinson's	33.0	Temp Pole Parkinson's2	35.4
BA9 Parkinson's2	28.7	Temp Pole Huntington's	57.8
BA9 Huntington's	58.2	Temp Pole PSP	8.8
BA9 Huntington's2	27.9	Temp Pole PSP2	8.9
BA9 PSP	17.1	Temp Pole Depression2	8.4
BA9 PSP2	3.6	Cing Gyr Control	51.1
BA9 Depression	6.8	Cing Gyr Control2	33.7
BA9 Depression2	5.8	Cing Gyr Alzheimer's	49.0
BA17 Control	9.4	Cing Gyr Alzheimer's2	11.1
BA17 Control2	14.2	Cing Gyr Parkinson's	61.1
BA17	4.4	Cing Gyr	42.0

Alzheimer's2		Parkinson's2	
BA17 Parkinson's	22.8	Cing Gyr Huntington's	77.4
BA17 Parkinson's2	4.9	Cing Gyr Huntington's2	38.2
BA17 Huntington's	14.6	Cing Gyr PSP	20.0
BA17 Huntington's2	8.8	Cing Gyr PSP2	25.0
BA17 Depression	7.2	Cing Gyr Depression	23.7
BA17 Depression2	4.6	Cing Gyr Depression2	11.3

CNS_neurodegeneration_v1.0 Summary: Ag2556

No difference was detected in the expression of the CG50273-01 gene in the postmortem brains of Alzheimer's patients when compared normal controls; however this panel demonstrates the expression of this gene in the CNS of an independent group of patients. See panel 1.3d for discussion of utility of this gene in the central nervous system.

Panel 1.3D Summary: Ag2556

Highest expression of the CG50273-01 gene is seen in fetal skeletal muscle (CT=31.4). Furthermore, this gene appears to be expressed at much higher levels in fetal skeletal muscle than in the adult (CT=40). This expression pattern suggests that the protein encoded by this gene may be involved in the development of this tissue. Furthermore, therapeutic application of the protein product may help in restoring muscle mass or function to weak or dystrophic muscle in the adult.

This gene also shows highly brain preferential expression. The CG50273-01 gene encodes a novel transmembrane protein. The combination of brain and skeletal muscle-preferential expression is consistent with a protein present in cholinergic synapses. Indeed, this gene shows homology to the cholinergic receptor CHRNA4 subunit. Therefore, this gene may be useful in the treatment of multiple sclerosis, ALS, or any disease in which the cholinergic system has been implicated (Alzheimer's disease).

Low but significant levels of expression are seen in renal and ovarian cancer cell lines. Thus, expression of this gene could potentially be used to differentiate between these samples and other samples on this panel or as a marker to detect the presence of these cancers.

Panel 2D Summary: Ag2556

- 5 Highest expression of the CG50273-01 gene is seen in normal kidney (CT=28.4).
Furthermore, this gene appears to be more highly expressed in normal kidney tissue adjacent to a kidney cancer, than in the cancer itself. Thus, expression of this gene could potentially be used as a marker to differentiate between normal and cancerous kidney tissue. Moreover, therapeutic modulation of the expression or function of this gene could potentially be useful in the treatment
10 of kidney cancer.

Panel 3D Summary: Ag2556

- Expression of the CG50273-01 gene is restricted to a few cell lines on this panel including two lung cancer cell lines, medulloblastoma, two renal and three pancreatic cancer cell lines as well as the cerebellum samples which reflect the brain expression seen in Panel 1.3D.

15 **Panel 4D Summary: Ag2556**

- The CG50273-01 gene appears to be preferentially expressed in normal thymus (CT=32.1). Since the thymus is involved in the development of the immune system, the transcript encoded by this gene could be used for detection of thymus/thymic cells as well as play a role in the homeostasis of the tissue and/or thymic/immune cells.

20 **Panel CNS_1 Summary: Ag2556**

- The widespread expression of the CG50273-01 gene in this panel confirms that it is expressed in the brain. Please see Panel 1.3D for discussion of potential utility of this gene in the central nervous system.

25 **NOV4 (CG50289-01: Serine Protease)**

Expression of gene CG50289-01 was assessed using the primer-probe sets Ag3600, Ag792 and Ag2555, described in Tables DA, DB and DC. Results of the RTQ-PCR runs are shown in Tables DD, DE, and DF.

Table DA. Probe Name Ag3600

Primers	Sequences	Length	Start Position
Forward	5'-agccaagcagcagtgactac-3' (SEQ ID NO:148)	20	507
Probe	TET-5'-accatccacgaggacatgctgtg-3'-TAMRA (SEQ ID NO:149)	23	527
Reverse	5'-aaatggcctttcctgttatgag-3' (SEQ ID NO:150)	22	560

5

Table DB. Probe Name Ag792

Primers	Sequences	Length	Start Position
Forward	5'-agccaagcagcagtgactac-3' (SEQ ID NO:151)	20	507
Probe	TET-5'-accatccacgaggacatgctgtg-3'-TAMRA (SEQ ID NO:152)	23	527
Reverse	5'-aaatggcctttcctgttatgag-3' (SEQ ID NO:153)	22	560

Table DC. Probe Name Ag2555

Primers	Sequences	Length	Start Position
Forward	5'-ctcataacaggaaaggccattt-3' (SEQ ID NO:154)	22	560
Probe	TET-5'-agactccaggggtcccctcgtct-3'-TAMRA (SEQ ID NO:155)	23	589
Reverse	5'-aggaaccaggtgccattta-3' (SEQ ID NO:156)	21	616

Table DD. General_screening_panel_v1.4

Tissue Name	Rel. Exp.(%) Ag3600, Run 217676536	Tissue Name	Rel. Exp.(%) Ag3600, Run 217676536
Adipose	0.0	Renal ca. TK-10	0.0
Melanoma* Hs688(A).T	0.0	Bladder	1.2
Melanoma* Hs688(B).T	0.0	Gastric ca. (liver met.) NCI-N87	0.0
Melanoma* M14	0.0	Gastric ca. KATO III	0.0
Melanoma*	0.0	Colon ca. SW-948	0.0

LOXIMVI			
Melanoma* SK-MEL-5	0.0	Colon ca. SW480	0.0
Squamous cell carcinoma SCC-4	0.0	Colon ca.* (SW480 met) SW620	0.0
Testis Pool	100.0	Colon ca. HT29	0.0
Prostate ca.* (bone met) PC-3	1.3	Colon ca. HCT-116	0.0
Prostate Pool	0.0	Colon ca. CaCo-2	3.7
Placenta	0.0	Colon cancer tissue	0.0
Uterus Pool	0.0	Colon ca. SW1116	0.0
Ovarian ca. OVCAR-3	0.0	Colon ca. Colo-205	0.0
Ovarian ca. SK-OV-3	0.0	Colon ca. SW-48	0.0
Ovarian ca. OVCAR-4	1.3	Colon Pool	2.6
Ovarian ca. OVCAR-5	0.0	Small Intestine Pool	0.6
Ovarian ca. IGROV-1	0.0	Stomach Pool	4.0
Ovarian ca. OVCAR-8	0.0	Bone Marrow Pool	3.0
Ovary	0.0	Fetal Heart	0.0
Breast ca. MCF-7	0.0	Heart Pool	0.4
Breast ca. MDA-MB-231	0.0	Lymph Node Pool	2.5
Breast ca. BT 549	0.0	Fetal Skeletal Muscle	0.0
Breast ca. T47D	0.0	Skeletal Muscle Pool	0.0
Breast ca. MDA-N	1.7	Spleen Pool	0.0
Breast Pool	1.3	Thymus Pool	2.6
Trachea	0.0	CNS cancer (glio/astro) U87-MG	0.0
Lung	0.0	CNS cancer (glio/astro) U-118-MG	0.0
Fetal Lung	0.0	CNS cancer (neuro;met) SK-N-AS	0.0
Lung ca. NCI-N417	0.0	CNS cancer (astro) SF-539	0.0
Lung ca. LX-1	0.0	CNS cancer (astro) SNB-75	0.0
Lung ca. NCI-H146	0.0	CNS cancer (glio) SNB-	0.0

			OVCAR-5		
Lymph node	0.0	0.0	Ovarian ca. OVCAR-8	0.0	0.0
Colorectal	0.0	3.4	Ovarian ca. IGROV-1	0.0	0.0
Stomach	0.0	3.7	Ovarian ca. (ascites) SK- OV-3	0.0	0.0
Small intestine	0.0	2.2	Uterus	0.0	0.0
Colon ca. SW480	0.0	0.0	Placenta	0.0	0.0
Colon ca.* SW620 (SW480 met)	0.0	0.0	Prostate	0.0	0.0
Colon ca. HT29	0.0	0.0	Prostate ca.* (bone met) PC- 3	0.0	0.0
Colon ca. HCT- 116	0.0	0.0	Testis	100.0	100.0
Colon ca. CaCo-2	0.0	0.0	Melanoma Hs688(A).T	0.0	0.0
CC Well to Mod Diff (ODO3866)	0.0	0.0	Melanoma* (met) Hs688(B).T	0.0	0.0
Colon ca. HCC- 2998	0.0	0.0	Melanoma UACC-62	0.0	0.0
Gastric ca. (liver met) NCI-N87	0.0	0.0	Melanoma M14	0.0	4.0
Bladder	0.0	1.0	Melanoma LOX IMVI	0.0	0.0
Trachea	0.0	0.0	Melanoma* (met) SK- MEL-5	0.0	0.0
Kidney	0.0	0.0	Adipose	0.0	0.0

CNS_neurodegeneration_v1.0 Summary: Ag3600

Expression of the CG50289-01 gene is low/undetectable in all samples on this panel (CT>35).

General_screening_panel_v1.4 Summary: Ag3600

Expression of the CG50289-01 gene is exclusive to the testis (CT=31.8). This gene encodes a serine protease homolog. Serine proteases are important in many aspects of cellular physiology including post-translational processing, protein degradation and cellular signalling. The exclusive expression of this gene in the testis suggests that the protein encoded by this gene
5 may be an excellent target for modulating male reproduction.

Panel 1.2 Summary: Ag792

Highest expression of the CG50289-01 gene is seen in the testis (CT=27.5), a result that is concordant with the results in General_screening_panel_v1.4. Low but significant expression is also seen in the pancreas. This expression profile suggests that the protein encoded by this gene
10 may be an excellent target for modulation of male reproduction and/or hormone release from the pancreas.

Panel 1.3D Summary: Ag792/Ag2555

Two experiments with the same probe and primer set show expression of the CG50289-01 gene to be exclusive to the testis (CTs=32-33). This result is in excellent agreement with the
15 results from Panel 1.2 and General_screening_panel_v1.4. Thus, this exclusive expression of this gene in the testis suggests that the protein encoded by this gene may be an excellent target for modulating male reproduction.

Panel 2D Summary: Ag2555

Expression of the CG50289-01 gene is low/undetectable in all samples on this panel
20 (CT>35).

Panel 4.1D Summary: Ag3600

Expression of the CG50289-01 gene is low/undetectable in all samples on this panel
(CT>35).

Panel 4D Summary: Ag2555

25 Expression of the CG50289-01 gene is low/undetectable in all samples on this panel
(CT>35).

NOV5a (CG50353-01: Wnt7a-like)

Expression of gene CG50353-01 was assessed using the primer-probe set Ag3093, described in Table EA. Results of the RTQ-PCR runs are shown in Tables EB, and EC.

Table EA. Probe Name Ag3093

Primers	Sequences	Length	Start Position
Forward	5'-ctgtgacctcatgtgctgtg-3' (SEQ ID NO:157)	20	909
Probe	TET-5'-gtggctacaacacccaccagtacgc-3'-TAMRA (SEQ ID NO:158)	25	932
Reverse	5'-acatagcagcaccagtggaa-3' (SEQ ID NO:159)	20	982

5

Table EB. Panel 1.3D

Tissue Name	Rel. Exp.(%) Ag3093, Run 167985246	Tissue Name	Rel. Exp.(%) Ag3093, Run 167985246
Liver adenocarcinoma	2.8	Kidney (fetal)	0.1
Pancreas	0.0	Renal ca. 786-0	0.2
Pancreatic ca. CAPAN 2	1.7	Renal ca. A498	0.0
Adrenal gland	0.0	Renal ca. RXF 393	0.4
Thyroid	0.0	Renal ca. ACHN	0.0
Salivary gland	0.0	Renal ca. UO-31	0.5
Pituitary gland	0.0	Renal ca. TK-10	0.0
Brain (fetal)	3.6	Liver	0.0
Brain (whole)	1.5	Liver (fetal)	0.0
Brain (amygdala)	1.8	Liver ca. (hepatoblast) HepG2	0.0
Brain (cerebellum)	0.9	Lung	0.2
Brain (hippocampus)	1.4	Lung (fetal)	0.9
Brain (substantia nigra)	0.9	Lung ca. (small cell) LX-1	0.0
Brain (thalamus)	0.0	Lung ca. (small cell) NCI-H69	0.2
Cerebral Cortex	3.5	Lung ca. (s.cell var.) SHP-77	0.0
Spinal cord	0.6	Lung ca. (large	0.0

		cell)NCI-H460	
glio/astro U87-MG	0.6	Lung ca. (non-sm. cell) A549	0.2
glio/astro U-118-MG	0.0	Lung ca. (non-s.cell) NCI-H23	0.0
astrocytoma SW1783	0.0	Lung ca. (non-s.cell) HOP-62	0.0
neuro*; met SK-N-AS	0.0	Lung ca. (non-s.cl) NCI-H522	0.0
astrocytoma SF-539	0.2	Lung ca. (squam.) SW 900	0.0
astrocytoma SNB-75	0.1	Lung ca. (squam.) NCI-H596	0.3
glioma SNB-19	0.0	Mammary gland	0.0
glioma U251	0.0	Breast ca.* (pl.ef) MCF-7	0.2
glioma SF-295	0.0	Breast ca.* (pl.ef) MDA-MB-231	0.0
Heart (Fetal)	0.0	Breast ca.* (pl. ef) T47D	0.0
Heart	0.0	Breast ca. BT-549	0.0
Skeletal muscle (Fetal)	0.0	Breast ca. MDA-N	0.0
Skeletal muscle	0.0	Ovary	0.0
Bone marrow	0.0	Ovarian ca. OVCAR- 3	0.1
Thymus	0.0	Ovarian ca. OVCAR- 4	37.1
Spleen	0.3	Ovarian ca. OVCAR- 5	0.7
Lymph node	0.0	Ovarian ca. OVCAR- 8	0.0
Colorectal	0.0	Ovarian ca. IGROV-1	6.8
Stomach	0.0	Ovarian ca. (ascites) SK-OV-3	100.0
Small intestine	0.0	Uterus	0.0
Colon ca. SW480	0.4	Placenta	0.0
Colon ca.* SW620 (SW480 met)	1.4	Prostate	0.0
Colon ca. HT29	0.0	Prostate ca.* (bone met) PC-3	2.0
Colon ca. HCT-116	0.0	Testis	0.3

Colon ca. CaCo-2	0.2	Melanoma Hs688(A).T	0.0
CC Well to Mod Diff (ODO3866)	0.0	Melanoma* (met) Hs688(B).T	0.0
Colon ca. HCC-2998	0.1	Melanoma UACC-62	0.0
Gastric ca. (liver met) NCI-N87	0.5	Melanoma M14	0.0
Bladder	0.0	Melanoma LOX IMVI	0.0
Trachea	0.1	Melanoma* (met) SK-MEL-5	0.0
Kidney	0.0	Adipose	0.2

Table EC. Panel 4D

Tissue Name	Rel. Exp.(%) Ag3093, Run 164392077	Tissue Name	Rel. Exp.(%) Ag3093, Run 164392077
Secondary Th1 act	0.0	HUVEC IL-1beta	0.0
Secondary Th2 act	0.0	HUVEC IFN gamma	0.0
Secondary Tr1 act	0.0	HUVEC TNF alpha + IFN gamma	0.0
Secondary Th1 rest	0.0	HUVEC TNF alpha + IL4	0.0
Secondary Th2 rest	0.0	HUVEC IL-11	0.0
Secondary Tr1 rest	0.0	Lung Microvascular EC none	0.0
Primary Th1 act	0.0	Lung Microvascular EC TNFalpha + IL-1beta	0.0
Primary Th2 act	0.0	Microvascular Dermal EC none	0.0
Primary Tr1 act	0.0	Microvascular Dermal EC TNFalpha + IL-1beta	0.0
Primary Th1 rest	0.0	Bronchial epithelium TNFalpha + IL1beta	57.4
Primary Th2 rest	0.0	Small airway epithelium none	17.7
Primary Tr1 rest	0.0	Small airway epithelium TNFalpha + IL-1beta	100.0

CD45RA CD4 lymphocyte act	0.0	Coronary artery SMC rest	0.0
CD45RO CD4 lymphocyte act	0.0	Coronary artery SMC TNFalpha + IL-1beta	0.0
CD8 lymphocyte act	0.0	Astrocytes rest	0.0
Secondary CD8 lymphocyte rest	0.0	Astrocytes TNFalpha + IL-1beta	0.0
Secondary CD8 lymphocyte act	0.0	KU-812 (Basophil) rest	0.0
CD4 lymphocyte none	4.9	KU-812 (Basophil) PMA/ionomycin	1.2
2ry Th1/Th2/Tr1_anti-CD95 CH11	0.0	CCD1106 (Keratinocytes) none	47.6
LAK cells rest	0.0	CCD1106 (Keratinocytes) TNFalpha + IL-1beta	33.7
LAK cells IL-2	0.0	Liver cirrhosis	1.4
LAK cells IL-2+IL-12	0.0	Lupus kidney	0.0
LAK cells IL-2+IFN gamma	0.0	NCI-H292 none	4.1
LAK cells IL-2+ IL-18	0.0	NCI-H292 IL-4	4.8
LAK cells PMA/ionomycin	0.0	NCI-H292 IL-9	1.8
NK Cells IL-2 rest	0.0	NCI-H292 IL-13	2.5
Two Way MLR 3 day	0.0	NCI-H292 IFN gamma	1.6
Two Way MLR 5 day	0.0	HPAEC none	0.0
Two Way MLR 7 day	0.0	HPAEC TNF alpha + IL-1 beta	0.0
PBMC rest	3.5	Lung fibroblast none	0.0
PBMC PWM	0.8	Lung fibroblast TNF alpha + IL-1 beta	0.0
PBMC PHA-L	0.0	Lung fibroblast IL-4	0.0
Ramos (B cell) none	0.0	Lung fibroblast IL-9	0.0
Ramos (B cell) ionomycin	0.0	Lung fibroblast IL-13	0.0
B lymphocytes PWM	0.0	Lung fibroblast IFN gamma	0.0
B lymphocytes CD40L and IL-4	0.0	Dermal fibroblast CCD1070 rest	0.0
EOL-1 dbcAMP	0.0	Dermal fibroblast CCD1070 TNF alpha	0.0
EOL-1 dbcAMP PMA/ionomycin	0.0	Dermal fibroblast CCD1070 IL-1 beta	0.0

Dendritic cells none	0.0	Dermal fibroblast IFN gamma	0.0
Dendritic cells LPS	0.0	Dermal fibroblast IL-4	0.0
Dendritic cells anti-CD40	0.0	IBD Colitis 2	0.0
Monocytes rest	0.0	IBD Crohn's	0.0
Monocytes LPS	0.0	Colon	1.0
Macrophages rest	0.0	Lung	2.0
Macrophages LPS	0.0	Thymus	0.0
HUVEC none	0.0	Kidney	0.0
HUVEC starved	0.0		

Panel 1.3D Summary: Ag3093

5 The CG50353-01 gene is expressed exclusively in two ovarian cancer cell lines, with highest expression in the SK-OV-3 cell line (CT=30.28). This cell line is unusual because it is derived from ascites. Thus, this gene could potentially be used as a marker for ovarian cancer, particularly ascites derived cancer or as a marker for ascites. Furthermore, antibodies or small molecule drugs could potentially be used in a therapeutic manner to modulate the activity of this gene in ovarian cancer.

10 Panel 2.2 Summary: Ag3093

Expression of the CG50353-01 gene is low/undetectable in all samples on this panel (CTs>35).

Panel 4D Summary: Ag3093

15 The CG50353-01 gene is expressed at the highest level in TNF alpha + IL-1 beta treated small airway epithelial cells (CT=32.6) as well as TNF alpha + IL-1 beta treated bronchial epithelial cells and CCD1106 keratinocytes (treated and non-treated). The presence of this transcript in keratinocytes suggests that this gene may be important in skin disorders including psoriasis. Expression in airway/bronchial cell types suggests that this gene may also be involved in inflammatory lung disorders that include chronic obstructive pulmonary disease, asthma,

allergy and emphysema. Therefore, therapeutic modalities that involve this gene or gene product may be beneficial in the treatment of these conditions.

NOV6a (CG50221-01: apical endosomal glycoprotein)

- 5 Expression of gene CG50221-01 was assessed using the primer-probe sets Ag2495 and Ag4806, described in Tables FA and FB. Results of the RTQ-PCR runs are shown in Table FC.

Table FA. Probe Name Ag2495

Primers	Sequences	Length	Start Position
Forward	5'-ctggcaccctgtctatactc-3' (SEQ ID NO:160)	20	1003
Probe	TET-5'-attccaagcctcaggcacctccaact-3'-TAMRA (SEQ ID NO:161)	26	1034
Reverse	5'-tgatagaagaccagccatctca-3' (SEQ ID NO:162)	22	1066

Table FB. Probe Name Ag4806

Primers	Sequences	Length	Start Position
Forward	5'-ctacgtggctctggatgatct-3' (SEQ ID NO:163)	21	2909
Probe	TET-5'-cctgccctcagccaggttctgt-3'-TAMRA (SEQ ID NO:164)	23	2947
Reverse	5'-acacaggccagactcaaaatc-3' (SEQ ID NO:165)	21	2970

Table FC. General_screening_panel_v1.4

Tissue Name	Rel. Exp.(%) Ag4806, Run 223204110	Tissue Name	Rel. Exp.(%) Ag4806, Run 223204110
Adipose	7.6	Renal ca. TK-10	4.4
Melanoma* Hs688(A).T	4.6	Bladder	13.7
Melanoma* Hs688(B).T	12.7	Gastric ca. (liver met.) NCI-N87	6.6
Melanoma* M14	27.7	Gastric ca. KATO III	0.0
Melanoma* LOXIMVI	0.0	Colon ca. SW-948	7.7
Melanoma* SK-MEL-5	0.0	Colon ca. SW480	9.6

Squamous cell carcinoma SCC-4	0.0	Colon ca. * (SW480 met) SW620	7.2
Testis Pool	0.0	Colon ca. HT29	15.0
Prostate ca. * (bone met) PC-3	0.0	Colon ca. HCT-116	15.2
Prostate Pool	3.6	Colon ca. CaCo-2	12.5
Placenta	4.7	Colon cancer tissue	15.8
Uterus Pool	0.0	Colon ca. SW1116	16.8
Ovarian ca. OVCAR-3	0.3	Colon ca. Colo-205	13.9
Ovarian ca. SK-OV-3	19.9	Colon ca. SW-48	0.0
Ovarian ca. OVCAR-4	0.0	Colon Pool	0.0
Ovarian ca. OVCAR-5	14.2	Small Intestine Pool	0.0
Ovarian ca. IGROV-1	24.1	Stomach Pool	1.3
Ovarian ca. OVCAR-8	23.2	Bone Marrow Pool	0.0
Ovary	0.7	Fetal Heart	17.0
Breast ca. MCF-7	6.7	Heart Pool	4.2
Breast ca. MDA-MB-231	65.1	Lymph Node Pool	3.5
Breast ca. BT 549	18.8	Fetal Skeletal Muscle	6.5
Breast ca. T47D	100.0	Skeletal Muscle Pool	11.8
Breast ca. MDA-N	8.7	Spleen Pool	18.7
Breast Pool	1.9	Thymus Pool	12.9
Trachea	0.0	CNS cancer (glio/astro) U87-MG	25.9
Lung	0.0	CNS cancer (glio/astro) U-118-MG	37.9
Fetal Lung	19.9	CNS cancer (neuro;met) SK-N-AS	9.3
Lung ca. NCI-N417	0.0	CNS cancer (astro) SF-539	3.2
Lung ca. LX-1	11.0	CNS cancer (astro) SNB-75	33.4
Lung ca. NCI-H146	0.0	CNS cancer (glio) SNB-19	11.0
Lung ca. SHP-77	11.4	CNS cancer (glio) SF-295	9.8

Lung ca. A549	33.7	Brain (Amygdala) Pool	9.0
Lung ca. NCI-H526	0.0	Brain (cerebellum)	22.4
Lung ca. NCI-H23	7.0	Brain (fetal)	14.4
Lung ca. NCI-H460	9.7	Brain (Hippocampus) Pool	8.4
Lung ca. HOP-62	7.9	Cerebral Cortex Pool	0.0
Lung ca. NCI-H522	0.0	Brain (Substantia nigra) Pool	18.9
Liver	40.1	Brain (Thalamus) Pool	8.2
Fetal Liver	5.1	Brain (whole)	3.5
Liver ca. HepG2	16.6	Spinal Cord Pool	7.8
Kidney Pool	11.5	Adrenal Gland	4.0
Fetal Kidney	16.7	Pituitary gland Pool	13.9
Renal ca. 786-0	25.7	Salivary Gland	0.8
Renal ca. A498	0.0	Thyroid (female)	1.8
Renal ca. ACHN	0.0	Pancreatic ca. CAPAN2	0.5
Renal ca. UO-31	8.8	Pancreas Pool	11.7

CNS_neurodegeneration_v1.0 Summary: Ag2495

Expression of the CG50221-01 gene is low/undetectable in all samples on this panel (CT>35).

General_screening_panel_v1.4 Summary: Ag4806

- 5 Expression of the CG50221-01 gene is highest in a breast cancer cell line (CT=31.5). This gene is also expressed in breast, ovarian and colon cancer cell lines at higher levels when compared to normal tissue samples. Hence, expression of this gene might be used as a marker to identify normal tissue from cancerous tissue in these organs.

- 10 There is relatively low level of expression in most endocrine (metabolic)-related tissues except for liver. Modulation of this gene or gene-product may therefore be beneficial in treating various abnormalities related to liver function. The higher levels of expression in adult liver (CT=32.7) when compared to fetal liver suggest that expression of this gene can also be used to differentiate fetal vs adult liver tissue. Conversely, higher levels of expression in fetal lung (CT=33) when compared to adult lung (CT=40) suggest involvement of this gene in the

development of the lung. Expression of this gene could also therefore be used to differentiate between fetal and adult lung tissue.

Panel 1.3D Summary: Ag2495

Expression of the CG50221-01 gene is low/undetectable in all samples on this panel
5 (CT>35).

Panel 2D Summary: Ag2495

Expression of the CG50221-01 gene is low/undetectable in all samples on this panel
(CT>35).

Panel 4D Summary: Ag2495

10 Expression of the CG50221-01 gene is low/undetectable in all samples on this panel
(CT>35).

NOV7a (CG50367-01: ADAM13-like)

15 Expression of gene CG50367-01 was assessed using the primer-probe set Ag2425,
described in Table GA. Results of the RTQ-PCR runs are shown in Tables GB, GC, and GD.

Table GA. Probe Name Ag2425

Primers	Sequences	Length	Start Position
Forward	5'-ggctcctgctgacatattc-3' (SEQ ID NO:166)	20	2342
Probe	TET-5'-catttaccctccaccatttctcccag-3'-TAMRA (SEQ ID NO:167)	26	2366
Reverse	5'-gctgggctcatgagagttct-3' (SEQ ID NO:168)	20	2398

Table GB. Panel 1.3D

Tissue Name	Rel. Exp.(%) Ag2425, Run 155561580	Tissue Name	Rel. Exp.(%) Ag2425, Run 155561580
Liver adenocarcinoma	0.0	Kidney (fetal)	3.9
Pancreas	1.8	Renal ca. 786-0	0.0
Pancreatic ca. CAPAN	0.0	Renal ca. A498	0.0

2			
Adrenal gland	0.9	Renal ca. RXF 393	0.0
Thyroid	2.7	Renal ca. ACHN	1.6
Salivary gland	1.1	Renal ca. UO-31	0.0
Pituitary gland	0.5	Renal ca. TK-10	0.0
Brain (fetal)	4.6	Liver	0.0
Brain (whole)	2.3	Liver (fetal)	1.2
Brain (amygdala)	4.2	Liver ca. (hepatoblast) HepG2	0.0
Brain (cerebellum)	0.0	Lung	2.8
Brain (hippocampus)	25.3	Lung (fetal)	17.9
Brain (substantia nigra)	2.4	Lung ca. (small cell) LX-1	0.0
Brain (thalamus)	9.4	Lung ca. (small cell) NCI-H69	0.0
Cerebral Cortex	1.5	Lung ca. (s.cell var.) SHP-77	1.0
Spinal cord	3.9	Lung ca. (large cell) NCI-H460	0.0
glio/astro U87-MG	0.0	Lung ca. (non-sm. cell) A549	1.7
glio/astro U-118-MG	1.1	Lung ca. (non-s.cell) NCI-H23	1.8
astrocytoma SW1783	0.0	Lung ca. (non-s.cell) HOP-62	0.0
neuro*; met SK-N-AS	0.0	Lung ca. (non-s.cl) NCI-H522	0.0
astrocytoma SF-539	0.0	Lung ca. (squam.) SW 900	0.0
astrocytoma SNB-75	0.0	Lung ca. (squam.) NCI-H596	0.0
glioma SNB-19	0.8	Mammary gland	13.5
glioma U251	0.0	Breast ca.* (pl.ef) MCF-7	0.0
glioma SF-295	0.0	Breast ca.* (pl.ef) MDA-MB-231	0.0
Heart (Fetal)	3.4	Breast ca.* (pl. ef) T47D	0.0
Heart	1.1	Breast ca. BT-549	1.6
Skeletal muscle (Fetal)	100.0	Breast ca. MDA-N	0.0
Skeletal muscle	0.9	Ovary	1.9

Bone marrow	3.3	Ovarian ca. OVCAR-3	0.0
Thymus	4.1	Ovarian ca. OVCAR-4	0.0
Spleen	2.7	Ovarian ca. OVCAR-5	0.0
Lymph node	4.6	Ovarian ca. OVCAR-8	0.0
Colorectal	5.9	Ovarian ca. IGROV-1	0.0
Stomach	7.3	Ovarian ca. (ascites) SK-OV-3	0.0
Small intestine	18.4	Uterus	37.4
Colon ca. SW480	0.0	Placenta	1.8
Colon ca.* SW620 (SW480 met)	0.0	Prostate	8.8
Colon ca. HT29	0.0	Prostate ca.* (bone met) PC-3	0.0
Colon ca. HCT-116	0.0	Testis	7.5
Colon ca. CaCo-2	0.0	Melanoma Hs688(A).T	5.0
CC Well to Mod Diff (ODO3866)	0.0	Melanoma* (met) Hs688(B).T	3.3
Colon ca. HCC-2998	0.0	Melanoma UACC-62	0.0
Gastric ca. (liver met) NCI-N87	0.0	Melanoma M14	0.0
Bladder	0.0	Melanoma LOX IMVI	0.0
Trachea	15.8	Melanoma* (met) SK-MEL-5	0.0
Kidney	1.8	Adipose	1.6

Table GC. Panel 2D

Tissue Name	Rel. Exp.(%) Ag2425, Run 155562155	Tissue Name	Rel. Exp.(%) Ag2425, Run 155562155
Normal Colon	100.0	Kidney Margin 8120608	0.0
CC Well to Mod Diff (ODO3866)	5.6	Kidney Cancer 8120613	0.0
CC Margin (ODO3866)	4.5	Kidney Margin 8120614	2.1

CC Gr.2 rectosigmoid (ODO3868)	20.7	Kidney Cancer 9010320	2.2
CC Margin (ODO3868)	21.9	Kidney Margin 9010321	6.1
CC Mod Diff (ODO3920)	6.7	Normal Uterus	49.3
CC Margin (ODO3920)	61.6	Uterine Cancer 064011	92.7
CC Gr.2 ascend colon (ODO3921)	1.0	Normal Thyroid	18.3
CC Margin (ODO3921)	6.2	Thyroid Cancer	0.0
CC from Partial Hepatectomy (ODO4309) Mets	0.0	Thyroid Cancer A302152	2.8
Liver Margin (ODO4309)	0.0	Thyroid Margin A302153	20.4
Colon mets to lung (OD04451-01)	0.0	Normal Breast	53.2
Lung Margin (OD04451-02)	0.0	Breast Cancer	0.0
Normal Prostate 6546-1	66.4	Breast Cancer (OD04590-01)	2.6
Prostate Cancer (OD04410)	25.9	Breast Cancer Mets (OD04590-03)	11.5
Prostate Margin (OD04410)	72.7	Breast Cancer Metastasis	0.0
Prostate Cancer (OD04720-01)	45.4	Breast Cancer	24.7
Prostate Margin (OD04720-02)	33.7	Breast Cancer	51.8
Normal Lung	84.1	Breast Cancer 9100266	3.1
Lung Met to Muscle (ODO4286)	9.4	Breast Margin 9100265	12.9
Muscle Margin (ODO4286)	0.0	Breast Cancer A209073	17.3
Lung Malignant Cancer (OD03126)	0.0	Breast Margin A2090734	99.3
Lung Margin (OD03126)	10.6	Normal Liver	0.0
Lung Cancer (OD04404)	0.0	Liver Cancer	4.0
Lung Margin (OD04404)	0.0	Liver Cancer 1025	4.9
Lung Cancer (OD04565)	13.7	Liver Cancer 1026	0.0
Lung Margin (OD04565)	10.6	Liver Cancer 6004-T	0.0
Lung Cancer (OD04237-	0.0	Liver Tissue 6004-N	8.5

01)			
Lung Margin (OD04237-02)	0.0	Liver Cancer 6005-T	0.0
Ocular Mel Met to Liver (ODO4310)	0.0	Liver Tissue 6005-N	0.0
Liver Margin (ODO4310)	0.0	Normal Bladder	11.1
Melanoma Metastasis	0.0	Bladder Cancer	3.1
Lung Margin (OD04321)	2.9	Bladder Cancer	14.6
Normal Kidney	9.7	Bladder Cancer (OD04718-01)	2.4
Kidney Ca, Nuclear grade 2 (OD04338)	0.0	Bladder Normal Adjacent (OD04718-03)	10.6
Kidney Margin (OD04338)	6.0	Normal Ovary	0.0
Kidney Ca Nuclear grade 1/2 (OD04339)	0.0	Ovarian Cancer	0.0
Kidney Margin (OD04339)	0.0	Ovarian Cancer (OD04768-07)	3.2
Kidney Ca, Clear cell type (OD04340)	0.0	Ovary Margin (OD04768-08)	6.0
Kidney Margin (OD04340)	4.0	Normal Stomach	12.7
Kidney Ca, Nuclear grade 3 (OD04348)	0.0	Gastric Cancer 9060358	9.9
Kidney Margin (OD04348)	6.7	Stomach Margin 9060359	0.0
Kidney Cancer (OD04622-01)	0.0	Gastric Cancer 9060395	39.2
Kidney Margin (OD04622-03)	7.4	Stomach Margin 9060394	26.4
Kidney Cancer (OD04450-01)	0.0	Gastric Cancer 9060397	6.2
Kidney Margin (OD04450-03)	0.0	Stomach Margin 9060396	3.3
Kidney Cancer 8120607	0.0	Gastric Cancer 064005	25.3

Table GD. Panel 4D

Tissue Name	Rel. Exp.(%) Ag2425, Run 155562267	Tissue Name	Rel. Exp.(%) Ag2425, Run 155562267
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Secondary Th1 act	0.0	HUVEC IL-1beta	0.0
Secondary Th2 act	0.0	HUVEC IFN gamma	0.0
Secondary Tr1 act	0.0	HUVEC TNF alpha + IFN gamma	0.0
Secondary Th1 rest	0.0	HUVEC TNF alpha + IL4	0.0
Secondary Th2 rest	0.0	HUVEC IL-11	0.0
Secondary Tr1 rest	0.0	Lung Microvascular EC none	0.0
Primary Th1 act	0.0	Lung Microvascular EC TNFalpha + IL-1beta	0.0
Primary Th2 act	0.0	Microvascular Dermal EC none	0.0
Primary Tr1 act	1.3	Microvascular Dermal EC TNFalpha + IL-1beta	0.0
Primary Th1 rest	0.0	Bronchial epithelium TNFalpha + IL1beta	0.0
Primary Th2 rest	0.0	Small airway epithelium none	0.0
Primary Tr1 rest	0.0	Small airway epithelium TNFalpha + IL-1beta	0.0
CD45RA CD4 lymphocyte act	1.8	Coronary artery SMC rest	0.0
CD45RO CD4 lymphocyte act	1.4	Coronary artery SMC TNFalpha + IL-1beta	0.0
CD8 lymphocyte act	0.0	Astrocytes rest	0.0
Secondary CD8 lymphocyte rest	0.0	Astrocytes TNFalpha + IL-1beta	0.0
Secondary CD8 lymphocyte act	0.0	KU-812 (Basophil) rest	0.0
CD4 lymphocyte none	1.3	KU-812 (Basophil) PMA/ionomycin	0.0
2ry Th1/Th2/Tr1_anti-CD95 CH11	3.9	CCD1106 (Keratinocytes) none	0.0
LAK cells rest	0.0	CCD1106 (Keratinocytes) TNFalpha + IL-1beta	0.0
LAK cells IL-2	0.0	Liver cirrhosis	4.9
LAK cells IL-2+IL-12	0.0	Lupus kidney	0.0
LAK cells IL-2+IFN gamma	0.0	NCI-H292 none	0.0
LAK cells IL-2+ IL-18	0.0	NCI-H292 IL-4	0.0
LAK cells	0.0	NCI-H292 IL-9	0.0

PMA/ionomycin			
NK Cells IL-2 rest	0.0	NCI-H292 IL-13	0.0
Two Way MLR 3 day	0.0	NCI-H292 IFN gamma	0.0
Two Way MLR 5 day	0.0	HPAEC none	0.0
Two Way MLR 7 day	0.0	HPAEC TNF alpha + IL-1 beta	0.0
PBMC rest	0.0	Lung fibroblast none	13.0
PBMC PWM	0.0	Lung fibroblast TNF alpha + IL-1 beta	2.7
PBMC PHA-L	0.0	Lung fibroblast IL-4	3.4
Ramos (B cell) none	0.0	Lung fibroblast IL-9	10.7
Ramos (B cell) ionomycin	0.0	Lung fibroblast IL-13	5.9
B lymphocytes PWM	0.0	Lung fibroblast IFN gamma	3.3
B lymphocytes CD40L and IL-4	0.0	Dermal fibroblast CCD1070 rest	23.7
EOL-1 dbcAMP	0.0	Dermal fibroblast CCD1070 TNF alpha	5.6
EOL-1 dbcAMP PMA/ionomycin	0.0	Dermal fibroblast CCD1070 IL-1 beta	12.5
Dendritic cells none	0.0	Dermal fibroblast IFN gamma	64.6
Dendritic cells LPS	0.0	Dermal fibroblast IL-4	100.0
Dendritic cells anti-CD40	0.0	IBD Colitis 2	0.0
Monocytes rest	0.0	IBD Crohn's	0.0
Monocytes LPS	0.0	Colon	28.3
Macrophages rest	0.0	Lung	21.6
Macrophages LPS	0.0	Thymus	0.0
HUVEC none	0.0	Kidney	0.0
HUVEC starved	0.0		

CNS_neurodegeneration_v1.0 Summary: Ag2425

Expression of the CG50367-01 gene is low/undetectable in all samples on this panel (CT>34.5).

Panel 1.3D Summary: Ag2425

Highest expression of the CG50367-01 gene is seen in fetal skeletal muscle (CT=31.1). This gene appears to be more highly expressed in fetal skeletal muscle when compared to expression in adult skeletal muscle (CT=40). Thus expression of this gene could be used to differentiate between fetal and adult skeletal muscle. Furthermore, the higher levels of expression
5 in the fetal source of the tissue suggest that the protein encoded by this gene may be involved in the development of the skeletal muscle in the fetus. Thus, therapeutic modulation of the expression or function of this gene may restore muscle mass or function to weak or dystrophic muscle in the adult.

This gene is expressed at a very low level in all the cancer cell lines used in this panel. The
10 absence of expression of this gene in the cancer cell lines suggests that modulation of the function of the gene product through the use of peptides, polypeptides, chimeric molecules or small molecule drugs, may be useful in the therapy of cancer.

This gene is a cell-surface metalloprotease expressed at low levels in the hippocampus. It may be useful in the treatment of diseases in which the hippocampus is involved, such as
15 Alzheimer's disease, Parkinson's disease, schizophrenia, bipolar disorder, or temporal lobe epilepsy.

Panel 2D Summary: Ag2425

The CG50367-01 gene is expressed at low levels in this panel, with highest expression in the colon (CT=32.2). Moderately higher levels of expression are seen in normal breast, uterine
20 and thyroid tissues compared to the adjacent cancers. Hence, expression of this gene might be used as a marker to identify normal tissue from cancerous tissue in these organs. Therapeutic modulation of the activity of the product of this gene, through the use of peptides, polypeptides, chimeric molecules or small molecule drugs, may be useful in the therapy of these cancers.

Panel 4D Summary: Ag2425

25 The CG50367-01 transcript is most highly expressed in dermal fibroblast upon treatment with either Il-4 or Ifn gamma (CTs=31-32) and at lower levels in resting dermal fibroblasts. This transcript is also expressed in lung fibroblasts and normal lung and thymus. This transcript encodes for a ADAM like protein, a member of membrane-anchored glycoproteins that have been

implicated in diverse cellular processes from cell cell interaction to shedding of cell surface proteases. The expression of this transcript in dermal and lung fibroblasts suggests that the protein encoded by this transcript might be involved in disease associated with fibrosis or fibroplasia. Modulation of the expression or the function of this molecule might be useful for the treatment of psoriasis, chronic obstructive pulmonary diseases and potentially for osteoarthritis and rheumatoid arthritis.

NOV8 (CG50321-01: Leucine Rich Containing F Box Protein)

Expression of gene CG50321-01 was assessed using the primer-probe set Ag2557, described in Table HA. Results of the RTQ-PCR runs are shown in Tables HB, HC and HD.

Table HA. Probe Name Ag2557

Primers	Sequences	Length	Start Position
Forward	5'-tgactttgaacttgcagacttg-3' (SEQ ID NO:169)	22	646
Probe	TET-5'-cttgcaaatacacagatgaaggtctca-3'-TAMRA (SEQ ID NO:170)	26	668
Reverse	5'-aggcacaagggtattgtaactt-3' (SEQ ID NO:171)	22	717

Table HB. CNS_neurodegeneration_v1.0

Tissue Name	Rel. Exp.(%) Ag2557, Run 206974725	Tissue Name	Rel. Exp.(%) Ag2557, Run 206974725
AD 1 Hippo	14.9	Control (Path) 3 Temporal Ctx	6.7
AD 2 Hippo	27.4	Control (Path) 4 Temporal Ctx	24.8
AD 3 Hippo	6.1	AD 1 Occipital Ctx	12.5
AD 4 Hippo	4.9	AD 2 Occipital Ctx (Missing)	0.0
AD 5 Hippo	92.7	AD 3 Occipital Ctx	5.0
AD 6 Hippo	49.0	AD 4 Occipital Ctx	16.7
Control 2 Hippo	28.5	AD 5 Occipital Ctx	15.6
Control 4 Hippo	8.4	AD 5 Occipital Ctx	48.0

Control (Path) 3 Hippo	6.9	Control 1 Occipital Ctx	3.6
AD 1 Temporal Ctx	15.8	Control 2 Occipital Ctx	71.2
AD 2 Temporal Ctx	29.9	Control 3 Occipital Ctx	12.4
AD 3 Temporal Ctx	3.8	Control 4 Occipital Ctx	5.7
AD 4 Temporal Ctx	18.7	Control (Path) 1 Occipital Ctx	100.0
AD 5 Inf Temporal Ctx	92.7	Control (Path) 2 Occipital Ctx	8.4
AD 5 Sup Temporal Ctx	32.1	Control (Path) 3 Occipital Ctx	2.1
AD 6 Inf Temporal Ctx	36.9	Control (Path) 4 Occipital Ctx	8.4
AD 6 Sup Temporal Ctx	37.1	Control 1 Parietal Ctx	7.2
Control 1 Temporal Ctx	6.6	Control 2 Parietal Ctx	33.7
Control 2 Temporal Ctx	51.1	Control 3 Parietal Ctx	17.7
Control 3 Temporal Ctx	13.2	Control (Path) 1 Parietal Ctx	95.3
Control 3 Temporal Ctx	6.8	Control (Path) 2 Parietal Ctx	17.6
Control (Path) 1 Temporal Ctx	66.0	Control (Path) 3 Parietal Ctx	5.1
Control (Path) 2 Temporal Ctx	29.3	Control (Path) 4 Parietal Ctx	39.8

Table HC. Panel 1.3D

Tissue Name	Rel. Exp.(%) Ag2557, Run 165640108	Tissue Name	Rel. Exp.(%) Ag2557, Run 165640108
Liver adenocarcinoma	23.8	Kidney (fetal)	12.7
Pancreas	5.4	Renal ca. 786-0	5.9
Pancreatic ca. CAPAN 2	20.7	Renal ca. A498	21.0
Adrenal gland	12.2	Renal ca. RXF 393	13.5
Thyroid	5.8	Renal ca. ACHN	10.5
Salivary gland	7.2	Renal ca. UO-31	6.3

Pituitary gland	8.5	Renal ca. TK-10	23.2
Brain (fetal)	31.4	Liver	4.0
Brain (whole)	55.1	Liver (fetal)	13.1
Brain (amygdala)	43.5	Liver ca. (hepatoblast) HepG2	7.5
Brain (cerebellum)	44.8	Lung	7.7
Brain (hippocampus)	42.3	Lung (fetal)	12.4
Brain (substantia nigra)	14.8	Lung ca. (small cell) LX-1	12.2
Brain (thalamus)	30.6	Lung ca. (small cell) NCI-H69	14.2
Cerebral Cortex	18.7	Lung ca. (s.cell var.) SHP-77	15.4
Spinal cord	11.2	Lung ca. (large cell) NCI-H460	54.0
glio/astro U87-MG	15.9	Lung ca. (non-sm. cell) A549	42.3
glio/astro U-118-MG	22.4	Lung ca. (non-s.cell) NCI-H23	17.3
astrocytoma SW1783	24.7	Lung ca. (non-s.cell) HOP-62	32.1
neuro*; met SK-N-AS	16.4	Lung ca. (non-s.cl) NCI-H522	14.2
astrocytoma SF-539	6.3	Lung ca. (squam.) SW 900	8.6
astrocytoma SNB-75	18.7	Lung ca. (squam.) NCI-H596	10.7
glioma SNB-19	22.7	Mammary gland	15.8
glioma U251	32.1	Breast ca.* (pl.ef) MCF-7	9.3
glioma SF-295	30.4	Breast ca.* (pl.ef) MDA-MB-231	16.3
Heart (Fetal)	3.7	Breast ca.* (pl. ef) T47D	24.5
Heart	7.9	Breast ca. BT-549	12.6
Skeletal muscle (Fetal)	2.3	Breast ca. MDA-N	4.4
Skeletal muscle	15.7	Ovary	5.8
Bone marrow	10.8	Ovarian ca. OVCAR- 3	10.4
Thymus	14.6	Ovarian ca. OVCAR- 4	6.2

Spleen	15.1	Ovarian ca. OVCAR-5	15.5
Lymph node	21.3	Ovarian ca. OVCAR-8	3.3
Colorectal	8.1	Ovarian ca. IGROV-1	2.7
Stomach	15.7	Ovarian ca. (ascites) SK-OV-3	28.9
Small intestine	20.9	Uterus	22.4
Colon ca. SW480	10.2	Placenta	8.5
Colon ca.* SW620 (SW480 met)	6.7	Prostate	6.8
Colon ca. HT29	1.0	Prostate ca.* (bone met) PC-3	17.6
Colon ca. HCT-116	10.7	Testis	27.0
Colon ca. CaCo-2	9.0	Melanoma Hs688(A).T	4.2
CC Well to Mod Diff (ODO3866)	7.7	Melanoma* (met) Hs688(B).T	5.9
Colon ca. HCC-2998	7.7	Melanoma UACC-62	9.7
Gastric ca. (liver met) NCI-N87	100.0	Melanoma M14	36.1
Bladder	14.9	Melanoma LOX IMVI	2.2
Trachea	9.9	Melanoma* (met) SK-MEL-5	4.1
Kidney	3.5	Adipose	7.4

Table HD. Panel 4D

Tissue Name	Rel. Exp.(%) Ag2557, Run 164393419	Tissue Name	Rel. Exp.(%) Ag2557, Run 164393419
Secondary Th1 act	27.4	HUVEC IL-1beta	4.8
Secondary Th2 act	19.8	HUVEC IFN gamma	19.8
Secondary Tr1 act	28.7	HUVEC TNF alpha + IFN gamma	3.9
Secondary Th1 rest	11.4	HUVEC TNF alpha + IL4	6.9
Secondary Th2 rest	17.9	HUVEC IL-11	8.0
Secondary Tr1 rest	19.3	Lung Microvascular EC none	19.5
Primary Th1 act	26.8	Lung Microvascular EC	13.7

		TNFalpha + IL-1beta	
Primary Th2 act	23.5	Microvascular Dermal EC none	35.6
Primary Tr1 act	36.9	Microvascular Dermal EC TNFalpha + IL-1beta	12.2
Primary Th1 rest	75.8	Bronchial epithelium TNFalpha + IL1beta	29.9
Primary Th2 rest	43.8	Small airway epithelium none	17.2
Primary Tr1 rest	34.2	Small airway epithelium TNFalpha + IL-1beta	47.6
CD45RA CD4 lymphocyte act	16.6	Coronary artery SMC rest	19.9
CD45RO CD4 lymphocyte act	36.3	Coronary artery SMC TNFalpha + IL-1beta	17.2
CD8 lymphocyte act	23.3	Astrocytes rest	21.8
Secondary CD8 lymphocyte rest	22.1	Astrocytes TNFalpha + IL-1beta	21.5
Secondary CD8 lymphocyte act	17.4	KU-812 (Basophil) rest	16.2
CD4 lymphocyte none	15.9	KU-812 (Basophil) PMA/ionomycin	56.6
2ry Th1/Th2/Tr1_anti-CD95 CH11	36.6	CCD1106 (Keratinocytes) none	14.6
LAK cells rest	21.5	CCD1106 (Keratinocytes) TNFalpha + IL-1beta	6.0
LAK cells IL-2	33.9	Liver cirrhosis	3.9
LAK cells IL-2+IL-12	23.2	Lupus kidney	3.9
LAK cells IL-2+IFN gamma	33.0	NCI-H292 none	46.3
LAK cells IL-2+ IL-18	35.4	NCI-H292 IL-4	57.8
LAK cells PMA/ionomycin	8.7	NCI-H292 IL-9	47.0
NK Cells IL-2 rest	23.3	NCI-H292 IL-13	28.5
Two Way MLR 3 day	20.3	NCI-H292 IFN gamma	24.3
Two Way MLR 5 day	16.7	HPAEC none	18.3
Two Way MLR 7 day	10.7	HPAEC TNF alpha + IL-1 beta	12.8
PBMC rest	26.6	Lung fibroblast none	12.8
PBMC PWM	85.3	Lung fibroblast TNF alpha + IL-1 beta	16.5

PBMC PHA-L	43.5	Lung fibroblast IL-4	13.6
Ramos (B cell) none	15.1	Lung fibroblast IL-9	13.7
Ramos (B cell) ionomycin	92.7	Lung fibroblast IL-13	9.6
B lymphocytes PWM	93.3	Lung fibroblast IFN gamma	11.2
B lymphocytes CD40L and IL-4	39.5	Dermal fibroblast CCD1070 rest	21.9
EOL-1 dbcAMP	65.5	Dermal fibroblast CCD1070 TNF alpha	52.9
EOL-1 dbcAMP PMA/ionomycin	58.2	Dermal fibroblast CCD1070 IL-1 beta	19.5
Dendritic cells none	18.9	Dermal fibroblast IFN gamma	13.8
Dendritic cells LPS	17.7	Dermal fibroblast IL-4	23.0
Dendritic cells anti-CD40	23.7	IBD Colitis 2	1.3
Monocytes rest	33.9	IBD Crohn's	2.8
Monocytes LPS	46.7	Colon	39.2
Macrophages rest	42.6	Lung	22.4
Macrophages LPS	26.6	Thymus	47.0
HUVEC none	12.9	Kidney	100.0
HUVEC starved	37.6		

CNS_neurodegeneration_v1.0 Summary: Ag2557

A small decrease is detected in the expression of the CG50321-01 gene in the postmortem brains of Alzheimer's patients when compared normal controls. This protein is an F-Box protein containing leucine-rich repeats; these proteins are involved in ubiquitination and proteosomal degradation of proteins. This gene is therefore an excellent drug target for the treatment of diseases involving protein precipitation including Alzheimer's disease, Huntington's disease, Parkinson's disease, progressive supranuclear palsy, or spinocerebellar ataxia.

Reference:

Ilyin GP, Riialand M, Pigeon C, Guguen-Guillouzo C. cDNA cloning and expression analysis of new members of the mammalian F-box protein family. Genomics 2000 Jul 1;67(1):40-

F-box proteins are critical components of the SCF ubiquitin-protein ligase complex and are involved in substrate recognition and recruitment for ubiquitination and consequent degradation by the proteasome. We have isolated cDNAs encoding a further 10 mammalian F-box proteins. Five of them (FBL3 to FBL7) share structural similarities with Skp2 and contain C-terminal leucine-rich repeats. The other 5 proteins have different putative protein-protein interaction motifs. Specifically, FBS and FBWD4 proteins contain Sec7 and WD40-repeat domains, respectively. The C-terminal region of FBA shares similarity with bacterial protein ApaG while FBG2 shows homology with the F-box protein NFB42. The marked differences in F-box gene expression in human tissues suggest their distinct role in ubiquitin-dependent protein degradation.

Panel 1.3D Summary: Ag2557

The CG50321-01 gene is expressed at a moderate to low level in most of the cell lines and tissues on this panel, with highest expression in a gastric cancer cell line (CT=30.4). This ubiquitous expression suggests a role in cell proliferation and survival.

There is a broad range of expression of this gene in endocrine (metabolic)-related tissues including adrenal, brain, GI tract, liver and skeletal muscle. Targeting this gene and/or gene-product may aid in the treatment of any number of endocrine or metabolically-related diseases, including obesity and diabetes.

This panel demonstrates the expression of this gene in the CNS in an independent group of patients. See panel CNS_Neurodegeneration for a discussion of utility of this gene in the central nervous system.

Panel 4D Summary: Ag 2557

Highest expression of the CG50321-01 transcript is found in kidney (CT=29.1). High levels of expression are also detected in activated B cells (primary B cells and B cell lymphoma), effector Th1 and the eosinophili cell line (EOL-1). At lower levels this transcript is expressed in a wide range of cell types of significance in the immune response in health and disease. This transcript encodes for leucine rich protein with a F-box domain. F-box proteins have been described as components of ubiquitin-ligase complexes, in which they bind substrates

for ubiquitin-mediated proteolysis. It is therefore theorized that they participate in the regulation of many processes, including cell division, transcription, signal transduction and development (ref 1). Targeting this gene and/or gene-product by small molecules may aid in the treatment of diseases associated with T and B cell or eosinophil involvement and lead to improvement of the symptoms of patients suffering from autoimmune, inflammatory and atopic diseases such as asthma, allergies, inflammatory bowel diseases, lupus erythematosus, rheumatoid arthritis, psoriasis and atopic skin diseases.

Reference:

1. Patton EE, Willems AR, Tyers M. Combinatorial control in ubiquitin-dependent proteolysis: don't Skp the F-box hypothesis.

Trends Genet 1998 Jun;14(6):236-43

The ubiquitin-dependent proteolytic pathway targets many key regulatory proteins for rapid intracellular degradation. Specificity in protein ubiquitination derives from E3 ubiquitin protein ligases, which recognize substrate proteins. Recently, analysis of the E3s that regulate cell division has revealed common themes in structure and function. One particularly versatile class of E3s, referred to as Skp1p-Cdc53p-F-box protein (SCF) complexes, utilizes substrate-specific adaptor subunits called F-box proteins to recruit various substrates to a core ubiquitination complex. A vast array of F-box proteins have been revealed by genome sequencing projects, and the early returns from genetic analysis in several organisms promise that F-box proteins will participate in the regulation of many processes, including cell division, transcription, signal transduction and development.

NOV9 (CG55902-01/AC079907.6: Steroid Binding Protein)

Expression of gene CG55902-01 was assessed using the primer-probe set Ag2626, described in Table JA. Please note that results from Panels 1.3D, 2.2 and 4D have been filed previously.

Table JA. Probe Name Ag2626

Primers	Sequences	Length	Start Position
Forward	5'-ttctcaatgagtttggcagc-3' (SEQ ID NO:172)	20	365
Probe	TET-5'-aacctggacttcaaggctgaagacca-3'-TAMRA (SEQ ID NO:173)	26	388
Reverse	5'-aaacctcagaaccctcctt-3' (SEQ ID NO:174)	20	430

Table JB. CNS_neurodegeneration_v1.0

CNS_neurodegeneration_v1.0 Summary: Ag2626

Expression of the CG55902-01 gene is low/undetectable in all samples on this panel (CT>34.5).

5

NOV10a and NOV10b (CG50307-01 and CG50307-02: Steroid Dehydrogenase-like)

Expression of gene CG50307-01 and variant CG50307-02 was assessed using the primer-probe sets Ag2248 and Ag2548, described in Tables KA and KB. Results of the RTQ-PCR runs are shown in Tables KC, KD, KE, KF, KG, KH, KI and KJ.

10

Table KA. Probe Name Ag2248

Primers	Sequences	Length	Start Position
Forward	5'-agcctacgctgaagagtttagc-3' (SEQ ID NO:175)	21	425
Probe	TET-5'-aagccgaggtctcaatataatcctga-3'-TAMRA (SEQ ID NO:176)	26	446
Reverse	5'-acctgcaacttctcctcggtt-3' (SEQ ID NO:177)	20	480

Table KB. Probe Name Ag2548

Primers	Sequences	Length	Start Position
Forward	5'-gacgttggcatcttggttaaata-3' (SEQ ID NO:178)	22	612
Probe	TET-5'-cgcagtatttcactcagctgtccgag-3'-TAMRA (SEQ ID NO:179)	26	658
Reverse	5'-ttatgatgtcccagagcttggtc-3' (SEQ ID NO:180)	22	684

Table KC. CNS_neurodegeneration_v1.0

Tissue Name	Rel. Exp.(%)	Rel. Exp.(%)	Tissue Name	Rel. Exp.(%)	Rel. Exp.(%)
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	Ag2248, Run 207928610	Ag2548, Run 208300028		Ag2248, Run 207928610	Ag2548, Run 208300028
AD 1 Hippo	20.2	14.7	Control (Path) 3 Temporal Ctx	4.4	4.1
AD 2 Hippo	27.2	46.7	Control (Path) 4 Temporal Ctx	37.6	37.9
AD 3 Hippo	5.6	6.9	AD 1 Occipital Ctx	11.0	20.0
AD 4 Hippo	10.8	11.4	AD 2 Occipital Ctx (Missing)	0.0	0.0
AD 5 Hippo	85.3	2.6	AD 3 Occipital Ctx	6.1	6.2
AD 6 Hippo	69.7	50.0	AD 4 Occipital Ctx	21.6	22.7
Control 2 Hippo	42.9	45.7	AD 5 Occipital Ctx	14.0	11.8
Control 4 Hippo	11.3	12.5	AD 5 Occipital Ctx	47.3	49.0
Control (Path) 3 Hippo	7.6	7.2	Control 1 Occipital Ctx	1.4	1.8
AD 1 Temporal Ctx	18.2	20.4	Control 2 Occipital Ctx	81.8	83.5
AD 2 Temporal Ctx	27.4	42.6	Control 3 Occipital Ctx	13.1	15.9
AD 3 Temporal Ctx	5.5	6.8	Control 4 Occipital Ctx	6.7	6.5
AD 4 Temporal Ctx	17.4	22.5	Control (Path) 1 Occipital Ctx	91.4	100.0
AD 5 Inf Temporal Ctx	89.5	99.3	Control (Path) 2 Occipital Ctx	11.8	9.7
AD 5 Sup Temporal	34.6	50.7	Control (Path) 3	1.6	2.0

Ctx			Occipital Ctx		
AD 6 Inf Temporal Ctx	42.9	42.0	Control (Path) 4 Occipital Ctx	15.5	15.1
AD 6 Sup Temporal Ctx	50.3	45.1	Control 1 Parietal Ctx	8.1	4.6
Control 1 Temporal Ctx	3.7	3.5	Control 2 Parietal Ctx	30.1	33.4
Control 2 Temporal Ctx	56.6	42.6	Control 3 Parietal Ctx	24.0	21.9
Control 3 Temporal Ctx	19.1	12.3	Control (Path) 1 Parietal Ctx	100.0	84.7
Control 3 Temporal Ctx	7.1	8.0	Control (Path) 2 Parietal Ctx	26.8	20.3
Control (Path) 1 Temporal Ctx	64.2	74.2	Control (Path) 3 Parietal Ctx	4.7	3.7
Control (Path) 2 Temporal Ctx	23.5	30.1	Control (Path) 4 Parietal Ctx	44.4	66.4

Table KD. Panel 1.3D

Tissue Name	Rel. Exp.(%) Ag2248, Run 159035206	Rel. Exp.(%) Ag2548, Run 162292266	Tissue Name	Rel. Exp.(%) Ag2248, Run 159035206	Rel. Exp.(%) Ag2548, Run 162292266
Liver adenocarcinoma	8.7	25.5	Kidney (fetal)	5.0	14.1
Pancreas	1.1	1.7	Renal ca. 786-0	5.3	7.5
Pancreatic ca. CAPAN 2	2.2	6.3	Renal ca. A498	10.2	9.0
Adrenal gland	6.6	6.0	Renal ca. RXF 393	1.5	9.0
Thyroid	9.0	19.3	Renal ca. ACHN	1.7	12.8
Salivary gland	2.9	3.7	Renal ca. UO-	5.4	15.1

			31		
Pituitary gland	19.8	16.2	Renal ca. TK-10	1.5	6.7
Brain (fetal)	28.3	14.3	Liver	1.3	0.4
Brain (whole)	22.7	25.2	Liver (fetal)	3.1	2.3
Brain (amygdala)	24.7	24.3	Liver ca. (hepatoblast) HepG2	8.1	18.7
Brain (cerebellum)	11.6	14.6	Lung	10.2	7.4
Brain (hippocampus)	100.0	45.1	Lung (fetal)	9.5	12.5
Brain (substantia nigra)	5.1	7.2	Lung ca. (small cell) LX-1	11.0	16.0
Brain (thalamus)	19.2	25.2	Lung ca. (small cell) NCI-H69	7.5	6.3
Cerebral Cortex	44.8	100.0	Lung ca. (s.cell var.) SHP-77	42.9	73.7
Spinal cord	4.8	14.9	Lung ca. (large cell) NCI-H460	2.7	10.1
glio/astro U87-MG	11.7	42.3	Lung ca. (non-sm. cell) A549	1.8	4.1
glio/astro U-118-MG	20.7	12.0	Lung ca. (non-s.cell) NCI-H23	11.7	28.5
astrocytoma SW1783	8.1	38.2	Lung ca. (non-s.cell) HOP-62	5.3	24.0
neuro*; met SK-N-AS	14.2	6.5	Lung ca. (non-s.cl) NCI-H522	5.0	15.1
astrocytoma SF-539	3.9	15.2	Lung ca. (squam.) SW 900	3.4	12.6
astrocytoma SNB-75	8.8	11.3	Lung ca. (squam.) NCI-H596	1.5	1.9
glioma SNB-19	4.1	20.0	Mammary gland	7.5	9.6
glioma U251	2.5	5.8	Breast ca.* (pl.ef) MCF-7	25.3	88.9
glioma SF-295	3.4	24.0	Breast ca.* (pl.ef) MDA-MB-231	21.8	6.4

Heart (Fetal)	9.7	35.1	Breast ca.* (pl. ef) T47D	13.6	29.3
Heart	3.6	11.4	Breast ca. BT-549	22.1	7.4
Skeletal muscle (Fetal)	8.2	44.1	Breast ca. MDA-N	5.7	11.1
Skeletal muscle	5.6	47.6	Ovary	5.4	26.6
Bone marrow	3.2	1.7	Ovarian ca. OVCAR-3	2.5	4.8
Thymus	3.5	40.6	Ovarian ca. OVCAR-4	0.6	3.6
Spleen	5.4	10.9	Ovarian ca. OVCAR-5	3.8	13.1
Lymph node	2.8	4.4	Ovarian ca. OVCAR-8	5.9	21.2
Colorectal	1.9	9.4	Ovarian ca. IGROV-1	1.4	3.1
Stomach	2.2	2.7	Ovarian ca. (ascites) SK-OV-3	5.3	13.1
Small intestine	5.0	7.3	Uterus	3.9	6.0
Colon ca. SW480	6.0	12.6	Placenta	5.2	8.8
Colon ca.* SW620 (SW480 met)	4.7	11.1	Prostate	2.0	6.7
Colon ca. HT29	2.6	7.1	Prostate ca.* (bone met) PC-3	5.4	9.7
Colon ca. HCT-116	9.5	22.4	Testis	7.7	24.8
Colon ca. CaCo-2	6.7	18.0	Melanoma Hs688(A).T	3.3	7.7
CC Well to Mod Diff (ODO3866)	4.8	13.2	Melanoma* (met) Hs688(B).T	1.2	6.9
Colon ca. HCC-2998	17.2	10.2	Melanoma UACC-62	1.5	5.6
Gastric ca. (liver met) NCI-N87	10.8	14.7	Melanoma M14	4.3	8.1
Bladder	2.6	11.0	Melanoma LOX IMVI	4.8	2.9
Trachea	6.4	13.8	Melanoma*	6.9	10.4

			(met) SK-MEL-5		
Kidney	1.7	14.1	Adipose	2.3	6.0

Table KE. Panel 2D

Tissue Name	Rel. Exp.(%) Ag2248, Run 159035545	Rel. Exp.(%) Ag2548, Run 162326203	Tissue Name	Rel. Exp.(%) Ag2248, Run 159035545	Rel. Exp.(%) Ag2548, Run 162326203
Normal Colon	49.3	39.5	Kidney Margin 8120608	4.7	6.3
CC Well to Mod Diff (ODO3866)	14.2	10.7	Kidney Cancer 8120613	7.1	14.0
CC Margin (ODO3866)	10.7	8.9	Kidney Margin 8120614	8.8	10.7
CC Gr.2 rectosigmoid (ODO3868)	6.6	5.9	Kidney Cancer 9010320	10.9	13.7
CC Margin (ODO3868)	5.8	6.9	Kidney Margin 9010321	9.7	18.4
CC Mod Diff (ODO3920)	38.4	21.5	Normal Uterus	6.5	8.0
CC Margin (ODO3920)	14.5	9.5	Uterine Cancer 064011	42.9	24.1
CC Gr.2 ascend colon (ODO3921)	25.5	15.8	Normal Thyroid	40.3	31.0
CC Margin (ODO3921)	7.7	5.9	Thyroid Cancer	21.0	21.0
CC from Partial Hepatectomy (ODO4309) Mets	32.5	28.5	Thyroid Cancer A302152	21.9	18.4
Liver Margin (ODO4309)	12.2	9.0	Thyroid Margin A302153	37.9	39.0
Colon mets to lung (OD04451- 01)	15.6	8.5	Normal Breast	18.9	23.8
Lung Margin (OD04451-02)	12.6	9.2	Breast Cancer	14.2	20.2
Normal Prostate 6546-1	6.6	57.4	Breast Cancer (OD04590-01)	100.0	100.0
Prostate Cancer	40.3	31.0	Breast Cancer	87.1	90.1

(OD04410)			Mets (OD04590-03)		
Prostate Margin (OD04410)	27.0	21.8	Breast Cancer Metastasis	37.6	37.4
Prostate Cancer (OD04720-01)	28.5	18.3	Breast Cancer	14.6	14.1
Prostate Margin (OD04720-02)	35.8	25.0	Breast Cancer	27.4	28.9
Normal Lung	56.6	39.0	Breast Cancer 9100266	46.7	41.5
Lung Met to Muscle (ODO4286)	33.4	22.7	Breast Margin 9100265	15.5	16.7
Muscle Margin (ODO4286)	22.1	12.3	Breast Cancer A209073	42.3	42.9
Lung Malignant Cancer (OD03126)	33.4	27.0	Breast Margin A2090734	21.3	17.2
Lung Margin (OD03126)	27.5	21.9	Normal Liver	5.4	4.6
Lung Cancer (OD04404)	13.3	14.9	Liver Cancer	3.8	3.0
Lung Margin (OD04404)	12.0	11.6	Liver Cancer 1025	4.2	2.3
Lung Cancer (OD04565)	14.1	14.3	Liver Cancer 1026	3.0	1.3
Lung Margin (OD04565)	6.9	11.0	Liver Cancer 6004-T	3.6	1.6
Lung Cancer (OD04237-01)	95.9	82.4	Liver Tissue 6004-N	11.7	9.0
Lung Margin (OD04237-02)	15.5	13.7	Liver Cancer 6005-T	2.2	2.9
Ocular Mel Met to Liver (ODO4310)	27.4	19.9	Liver Tissue 6005-N	4.4	3.8
Liver Margin (ODO4310)	5.1	3.4	Normal Bladder	26.6	16.0
Melanoma Metastasis	24.8	18.8	Bladder Cancer	5.0	3.0
Lung Margin (OD04321)	23.8	20.0	Bladder Cancer	17.1	8.8
Normal Kidney	40.1	48.0	Bladder Cancer	22.2	15.5

			(OD04718-01)		
Kidney Ca, Nuclear grade 2 (OD04338)	30.6	41.8	Bladder Normal Adjacent (OD04718-03)	21.2	15.6
Kidney Margin (OD04338)	16.4	15.9	Normal Ovary	12.6	8.8
Kidney Ca Nuclear grade 1/2 (OD04339)	11.3	15.8	Ovarian Cancer	21.6	16.5
Kidney Margin (OD04339)	19.6	24.5	Ovarian Cancer (OD04768-07)	40.1	33.9
Kidney Ca, Clear cell type (OD04340)	20.4	30.8	Ovary Margin (OD04768-08)	11.3	4.0
Kidney Margin (OD04340)	18.4	13.9	Normal Stomach	12.2	8.8
Kidney Ca, Nuclear grade 3 (OD04348)	13.3	6.1	Gastric Cancer 9060358	5.0	3.0
Kidney Margin (OD04348)	21.2	19.3	Stomach Margin 9060359	16.0	11.0
Kidney Cancer (OD04622-01)	19.3	19.2	Gastric Cancer 9060395	16.3	12.6
Kidney Margin (OD04622-03)	4.4	5.3	Stomach Margin 9060394	13.9	10.6
Kidney Cancer (OD04450-01)	23.8	27.0	Gastric Cancer 9060397	24.0	12.1
Kidney Margin (OD04450-03)	15.2	20.0	Stomach Margin 9060396	6.4	7.1
Kidney Cancer 8120607	5.6	4.2	Gastric Cancer 064005	37.1	20.3

Table KF. Panel 3D

Tissue Name	Rel. Exp.(%) Ag2548, Run 164886193	Tissue Name	Rel. Exp.(%) Ag2548, Run 164886193
Daoy- Medulloblastoma	8.7	Ca Ski- Cervical epidermoid	10.6

		carcinoma (metastasis)	
TE671- Medulloblastoma	10.7	ES-2- Ovarian clear cell carcinoma	11.3
D283 Med-Medulloblastoma	40.6	Ramos- Stimulated with PMA/ionomycin 6h	2.0
PFSK-1- Primitive Neuroectodermal	9.0	Ramos- Stimulated with PMA/ionomycin 14h	8.8
XF-498- CNS	9.3	MEG-01- Chronic myelogenous leukemia (megakaryoblast)	11.5
SNB-78- Glioma	12.9	Raji- Burkitt's lymphoma	4.5
SF-268- Glioblastoma	9.4	Daudi- Burkitt's lymphoma	12.0
T98G- Glioblastoma	13.7	U266- B-cell plasmacytoma	28.1
SK-N-SH- Neuroblastoma (metastasis)	14.9	CA46- Burkitt's lymphoma	9.2
SF-295- Glioblastoma	9.9	RL- non-Hodgkin's B-cell lymphoma	2.2
Cerebellum	21.5	JM1- pre-B-cell lymphoma	6.3
Cerebellum	6.0	Jurkat- T cell leukemia	18.7
NCI-H292- Mucoepidermoid lung carcinoma	25.7	TF-1- Erythroleukemia	9.7
DMS-114- Small cell lung cancer	16.3	HUT 78- T-cell lymphoma	17.1
DMS-79- Small cell lung cancer	100.0	U937- Histiocytic lymphoma	11.2
NCI-H146- Small cell lung cancer	20.9	KU-812- Myelogenous leukemia	5.3
NCI-H526- Small cell lung cancer	36.6	769-P- Clear cell renal carcinoma	6.2
NCI-N417- Small cell lung cancer	9.7	Caki-2- Clear cell renal carcinoma	8.1
NCI-H82- Small cell lung cancer	14.2	SW 839- Clear cell renal carcinoma	2.9
NCI-H157- Squamous cell lung cancer (metastasis)	19.6	G401- Wilms' tumor	8.8
NCI-H1155- Large cell lung cancer	34.6	Hs766T- Pancreatic carcinoma (LN metastasis)	13.3
NCI-H1299- Large cell lung cancer	19.9	CAPAN-1- Pancreatic adenocarcinoma (liver metastasis)	7.7
NCI-H727- Lung	14.2	SU86.86- Pancreatic	10.0

carcinoid		carcinoma (liver metastasis)	
NCI-UMC-11- Lung carcinoid	12.6	BxPC-3- Pancreatic adenocarcinoma	4.3
LX-1- Small cell lung cancer	20.0	HPAC- Pancreatic adenocarcinoma	6.6
Colo-205- Colon cancer	15.8	MIA PaCa-2- Pancreatic carcinoma	4.6
KM12- Colon cancer	9.3	CFPAC-1- Pancreatic ductal adenocarcinoma	19.5
KM20L2- Colon cancer	3.0	PANC-1- Pancreatic epithelioid ductal carcinoma	9.5
NCI-H716- Colon cancer	19.1	T24- Bladder carcinoma (transitional cell)	9.9
SW-48- Colon adenocarcinoma	7.9	5637- Bladder carcinoma	4.7
SW1H16- Colon adenocarcinoma	7.4	HT-1197- Bladder carcinoma	6.1
LS174T- Colon adenocarcinoma	4.6	UM-UC-3- Bladder carcinoma (transitional cell)	2.8
SW-948- Colon adenocarcinoma	1.1	A204- Rhabdomyosarcoma	3.4
SW-480- Colon adenocarcinoma	2.7	HT-1080- Fibrosarcoma	10.7
NCI-SNU-5- Gastric carcinoma	9.3	MG-63- Osteosarcoma	1.3
KATO III- Gastric carcinoma	24.0	SK-LMS-1- Leiomyosarcoma (vulva)	9.5
NCI-SNU-16- Gastric carcinoma	9.5	SJRH30- Rhabdomyosarcoma (met to bone marrow)	10.2
NCI-SNU-1- Gastric carcinoma	12.2	A431- Epidermoid carcinoma	5.0
RF-1- Gastric adenocarcinoma	5.1	WM266-4- Melanoma	10.5
RF-48- Gastric adenocarcinoma	8.1	DU 145- Prostate carcinoma (brain metastasis)	0.0
MKN-45- Gastric carcinoma	5.3	MDA-MB-468- Breast adenocarcinoma	20.7
NCI-N87- Gastric carcinoma	7.4	SCC-4- Squamous cell carcinoma of tongue	0.0
OVCAR-5- Ovarian carcinoma	2.7	SCC-9- Squamous cell carcinoma of tongue	0.0
RL95-2- Uterine	3.8	SCC-15- Squamous cell	0.0

carcinoma		carcinoma of tongue	
HeLaS3- Cervical adenocarcinoma	10.7	CAL 27- Squamous cell carcinoma of tongue	5.5

Table KG. Panel 4D

Tissue Name	Rel. Exp.(%) Ag2248, Run 159034717	Tissue Name	Rel. Exp.(%) Ag2248, Run 159034717
Secondary Th1 act	27.2	HUVEC IL-1beta	8.4
Secondary Th2 act	33.4	HUVEC IFN gamma	14.4
Secondary Tr1 act	37.4	HUVEC TNF alpha + IFN gamma	7.4
Secondary Th1 rest	11.7	HUVEC TNF alpha + IL4	6.6
Secondary Th2 rest	10.4	HUVEC IL-11	11.8
Secondary Tr1 rest	12.5	Lung Microvascular EC none	9.9
Primary Th1 act	28.5	Lung Microvascular EC TNFalpha + IL-1beta	18.2
Primary Th2 act	29.3	Microvascular Dermal EC none	28.9
Primary Tr1 act	29.3	Microvascular Dermal EC TNFalpha + IL-1beta	20.2
Primary Th1 rest	62.4	Bronchial epithelium TNFalpha + IL1beta	20.7
Primary Th2 rest	39.8	Small airway epithelium none	6.9
Primary Tr1 rest	15.3	Small airway epithelium TNFalpha + IL-1beta	40.3
CD45RA CD4 lymphocyte act	18.6	Coronary artery SMC rest	15.4
CD45RO CD4 lymphocyte act	20.9	Coronary artery SMC TNFalpha + IL-1beta	6.8
CD8 lymphocyte act	14.7	Astrocytes rest	20.0
Secondary CD8 lymphocyte rest	11.9	Astrocytes TNFalpha + IL-1beta	15.8
Secondary CD8 lymphocyte act	19.9	KU-812 (Basophil) rest	8.1
CD4 lymphocyte none	8.2	KU-812 (Basophil) PMA/ionomycin	20.2

2ry Th1/Th2/Tr1_anti-CD95 CH11	17.4	CCD1106 (Keratinocytes) none	11.5
LAK cells rest	19.2	CCD1106 (Keratinocytes) TNFalpha + IL-1beta	5.3
LAK cells IL-2	18.2	Liver cirrhosis	2.4
LAK cells IL-2+IL-12	11.0	Lupus kidney	1.8
LAK cells IL-2+IFN gamma	19.5	NCI-H292 none	39.5
LAK cells IL-2+ IL-18	17.7	NCI-H292 IL-4	38.2
LAK cells PMA/ionomycin	3.6	NCI-H292 IL-9	40.1
NK Cells IL-2 rest	11.0	NCI-H292 IL-13	18.2
Two Way MLR 3 day	19.2	NCI-H292 IFN gamma	14.7
Two Way MLR 5 day	8.9	HPAEC none	19.2
Two Way MLR 7 day	6.7	HPAEC TNF alpha + IL-1 beta	28.5
PBMC rest	5.8	Lung fibroblast none	17.4
PBMC PWM	40.6	Lung fibroblast TNF alpha + IL-1 beta	17.1
PBMC PHA-L	25.9	Lung fibroblast IL-4	30.4
Ramos (B cell) none	26.6	Lung fibroblast IL-9	20.2
Ramos (B cell) ionomycin	100.0	Lung fibroblast IL-13	16.3
B lymphocytes PWM	35.6	Lung fibroblast IFN gamma	28.1
B lymphocytes CD40L and IL-4	29.7	Dermal fibroblast CCD1070 rest	32.3
EOL-1 dbcAMP	10.5	Dermal fibroblast CCD1070 TNF alpha	57.0
EOL-1 dbcAMP PMA/ionomycin	7.5	Dermal fibroblast CCD1070 IL-1 beta	15.3
Dendritic cells none	11.6	Dermal fibroblast IFN gamma	12.1
Dendritic cells LPS	7.7	Dermal fibroblast IL-4	20.3
Dendritic cells anti-CD40	9.6	IBD Colitis 2	2.3
Monocytes rest	12.6	IBD Crohn's	2.6
Monocytes LPS	21.0	Colon	11.5
Macrophages rest	24.5	Lung	16.2
Macrophages LPS	14.8	Thymus	38.7
HUVEC none	25.9	Kidney	71.2

HUVEC starved	40.9		
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Table KH. Panel 5 Islet

Tissue Name	Rel. Exp.(%) Ag2248, Run 233070521	Tissue Name	Rel. Exp.(%) Ag2248, Run 233070521
97457_Patient-02go_adipose	23.7	94709_Donor 2 AM - A_adipose	10.5
97476_Patient-07sk_skeletal muscle	12.3	94710_Donor 2 AM - B_adipose	5.0
97477_Patient-07ut_uterus	18.9	94711_Donor 2 AM - C_adipose	5.3
97478_Patient-07pl_placenta	35.6	94712_Donor 2 AD - A_adipose	14.5
99167_Bayer Patient 1	25.0	94713_Donor 2 AD - B_adipose	25.2
97482_Patient-08ut_uterus	23.2	94714_Donor 2 AD - C_adipose	18.7
97483_Patient-08pl_placenta	25.5	94742_Donor 3 U - A_Mesenchymal Stem Cells	7.4
97486_Patient-09sk_skeletal muscle	0.7	94743_Donor 3 U - B_Mesenchymal Stem Cells	11.2
97487_Patient-09ut_uterus	23.0	94730_Donor 3 AM - A_adipose	14.6
97488_Patient-09pl_placenta	15.3	94731_Donor 3 AM - B_adipose	4.5
97492_Patient-10ut_uterus	15.1	94732_Donor 3 AM - C_adipose	10.5
97493_Patient-10pl_placenta	52.9	94733_Donor 3 AD - A_adipose	40.1
97495_Patient-11go_adipose	9.1	94734_Donor 3 AD - B_adipose	16.0
97496_Patient-11sk_skeletal muscle	10.2	94735_Donor 3 AD - C_adipose	14.0
97497_Patient-11ut_uterus	21.8	77138_Liver_HepG2untreated	100.0
97498_Patient-11pl_placenta	36.3	73556_Heart_Cardiac stromal cells (primary)	9.5

97500_Patient-12go_adipose	21.0	81735_Small Intestine	8.7
97501_Patient-12sk_skeletal muscle	35.4	72409_Kidney_Proximal Convoluted Tubule	16.7
97502_Patient-12ut_uterus	15.5	82685_Small intestine_Duodenum	5.1
97503_Patient-12pl_placenta	9.5	90650_Adrenal_Adrenocortical adenoma	18.0
94721_Donor 2 U - A_Mesenchymal Stem Cells	8.3	72410_Kidney_HRCE	42.0
94722_Donor 2 U - B_Mesenchymal Stem Cells	8.3	72411_Kidney_HRE	27.0
94723_Donor 2 U - C_Mesenchymal Stem Cells	20.4	73139_Uterus_Uterine smooth muscle cells	41.5

Table KI. Panel 5D

Tissue Name	Rel. Exp.(%) Ag2248, Run 166667616	Tissue Name	Rel. Exp.(%) Ag2248, Run 166667616
97457_Patient-02go_adipose	44.1	94709_Donor 2 AM - A_adipose	24.3
97476_Patient-07sk_skeletal muscle	13.6	94710_Donor 2 AM - B_adipose	7.0
97477_Patient-07ut_uterus	42.0	94711_Donor 2 AM - C_adipose	3.1
97478_Patient-07pl_placenta	64.6	94712_Donor 2 AD - A_adipose	13.9
97481_Patient-08sk_skeletal muscle	29.7	94713_Donor 2 AD - B_adipose	39.2
97482_Patient-08ut_uterus	19.5	94714_Donor 2 AD - C_adipose	35.4
97483_Patient-08pl_placenta	42.0	94742_Donor 3 U - A_Mesenchymal Stem Cells	17.2
97486_Patient-09sk_skeletal muscle	7.3	94743_Donor 3 U - B_Mesenchymal Stem Cells	6.4
97487_Patient-09ut_uterus	26.2	94730_Donor 3 AM - A_adipose	10.0
97488_Patient-	31.0	94731_Donor 3 AM - B_adipose	6.5

09pl_placenta			
97492_Patient-10ut_uterus	30.4	94732_Donor 3 AM - C_adipose	7.6
97493_Patient-10pl_placenta	100.0	94733_Donor 3 AD - A_adipose	19.5
97495_Patient-11go adipose	13.1	94734_Donor 3 AD - B_adipose	25.3
97496_Patient-11sk_skeletal muscle	9.3	94735_Donor 3 AD - C_adipose	9.1
97497_Patient-11ut_uterus	30.1	77138_Liver_HepG2untreated	51.1
97498_Patient-11pl_placenta	25.0	73556_Heart_Cardiac stromal cells (primary)	4.1
97500_Patient-12go adipose	24.0	81735_Small Intestine	13.2
97501_Patient-12sk_skeletal muscle	70.7	72409_Kidney_Proximal Convoluted Tubule	21.6
97502_Patient-12ut_uterus	13.8	82685_Small intestine_Duodenum	3.7
97503_Patient-12pl_placenta	8.5	90650_Adrenal_Adrenocortical adenoma	10.9
94721_Donor 2 U - A_Mesenchymal Stem Cells	12.4	72410_Kidney_HRCE	22.5
94722_Donor 2 U - B_Mesenchymal Stem Cells	19.9	72411_Kidney_HRE	25.3
94723_Donor 2 U - C_Mesenchymal Stem Cells	23.5	73139_Uterus_Uterine smooth muscle cells	28.7

Table KJ. Panel CNS_1

Tissue Name	Rel. Exp.(%) Ag2248, Run 171649039	Tissue Name	Rel. Exp.(%) Ag2248, Run 171649039
BA4 Control	39.8	BA17 PSP	29.1
BA4 Control2	41.8	BA17 PSP2	13.1
BA4 Alzheimer's2	10.7	Sub Nigra Control	22.8
BA4 Parkinson's	49.7	Sub Nigra Control2	42.6
BA4 Parkinson's2	100.0	Sub Nigra Alzheimer's2	15.1

BA4 Huntington's	42.9	Sub Nigra Parkinson's2	54.7
BA4 Huntington's2	14.5	Sub Nigra Huntington's	58.6
BA4 PSP	4.4	Sub Nigra Huntington's2	48.6
BA4 PSP2	20.0	Sub Nigra PSP2	5.1
BA4 Depression	11.7	Sub Nigra Depression	8.7
BA4 Depression2	7.0	Sub Nigra Depression2	11.4
BA7 Control	71.2	Glob Palladus Control	10.4
BA7 Control2	30.4	Glob Palladus Control2	5.9
BA7 Alzheimer's2	9.2	Glob Palladus Alzheimer's	13.8
BA7 Parkinson's	17.7	Glob Palladus Alzheimer's2	2.7
BA7 Parkinson's2	60.3	Glob Palladus Parkinson's	50.0
BA7 Huntington's	44.8	Glob Palladus Parkinson's2	10.7
BA7 Huntington's2	49.0	Glob Palladus PSP	6.9
BA7 PSP	34.4	Glob Palladus PSP2	7.2
BA7 PSP2	34.2	Glob Palladus Depression	4.6
BA7 Depression	16.4	Temp Pole Control	14.6
BA9 Control	35.8	Temp Pole Control2	51.1
BA9 Control2	59.9	Temp Pole Alzheimer's	7.7
BA9 Alzheimer's	4.0	Temp Pole Alzheimer's2	9.0
BA9 Alzheimer's2	20.0	Temp Pole Parkinson's	18.6
BA9 Parkinson's	36.6	Temp Pole Parkinson's2	48.6
BA9 Parkinson's2	57.8	Temp Pole Huntington's	44.4
BA9 Huntington's	57.8	Temp Pole PSP	2.6

BA9 Huntington's2	24.1	Temp Pole PSP2	5.7
BA9 PSP	12.5	Temp Pole Depression2	11.0
BA9 PSP2	3.8	Cing Gyr Control	63.7
BA9 Depression	7.3	Cing Gyr Control2	37.4
BA9 Depression2	18.6	Cing Gyr Alzheimer's	28.5
BA17 Control	40.1	Cing Gyr Alzheimer's2	14.3
BA17 Control2	35.1	Cing Gyr Parkinson's	32.8
BA17 Alzheimer's2	6.8	Cing Gyr Parkinson's2	55.1
BA17 Parkinson's	39.0	Cing Gyr Huntington's	79.6
BA17 Parkinson's2	51.1	Cing Gyr Huntington's2	19.2
BA17 Huntington's	31.6	Cing Gyr PSP	14.2
BA17 Huntington's2	20.2	Cing Gyr PSP2	10.8
BA17 Depression	11.3	Cing Gyr Depression	4.8
BA17 Depression2	29.5	Cing Gyr Depression2	19.3

CNS_neurodegeneration_v1.0 Summary: Ag2248/Ag2548

Two experiments with two different probe and primer sets produce results that are in very good agreement, with highest expression of the CG50307-01 gene in the occipital and parietal cortex (CTs=27-29) of the brains of control patients. While this gene does not appear to be differentially expressed in Alzheimer's disease, these results confirm the expression of this gene at moderate to high levels in the brains of an independent group of patients. Please see Panel 1.3d for discussion of utility in the central nervous system.

Panel 1.3D Summary: Ag2248/Ag2548

Two experiments with two different probe and primer sets show widespread expression of the CG50307-01 gene, with highest expression seen in regions of the brain (CTs=28-29).

This gene encodes a protein that is homologous to steroid dehydrogenase. Steroid treatment is used in a number of clinical conditions including Alzheimer's disease (estrogen), treatment of symptoms associated with menopause (estrogen), multiple sclerosis (glucocorticoids), and spinal cord injury (methylprednisolone). Treatment with an antagonist of this gene product, or reduction of the levels of this gene product could slow steroid degradation and lower the necessary amount given for therapeutic effect, thus reducing peripheral side effects.

This gene is moderately expressed in a variety of metabolic tissues including pancreas, adrenal, thyroid, pituitary, adult and fetal heart, adult and fetal skeletal muscle, fetal liver, and adipose. Thus, this gene product may be a small molecule drug target for the treatment of metabolic disease, including obesity and Types 1 and 2 diabetes.

The ubiquitous expression of this gene in this panel also suggests that the protein encoded by this gene plays a role in cell survival and proliferation for a majority of cell types. Furthermore, there are significant levels of expression in the lung cancer cell line SHP-77. Thus, expression of this gene could potentially be used as a diagnostic marker for some forms of lung cancer. Modulation of the gene product may also play a role in treating lung cancer.

References:

Matsumoto T, Tamaki T, Kawakami M, Yoshida M, Ando M, Yamada H. Early complications of high-dose methylprednisolone sodium succinate treatment in the follow-up of acute cervical spinal cord injury. Spine 2001 Feb 15;26(4):426-30

STUDY DESIGN: A prospective, randomized, and double-blind study comparing high-dose methylprednisolone sodium succinate (MPSS) with placebo, in the treatment of patients with acute cervical spinal cord injury. OBJECTIVES: To evaluate the complications of high-dose MPSS in patients with acute cervical spinal cord injury when administered within 8 hours of injury. SUMMARY OF BACKGROUND DATA: High-dose therapy with MPSS has been demonstrated to improve the recovery of motor function in patients with acute cervical spinal cord injury. However, little is known about the follow-up complications. METHODS: Forty-six patients, 42 men and 4 women (mean age, 60.6 years; range, 18-84), were included in the study: 23 in the MPSS group and 23 in the placebo group. They were treated without surgery for spinal

cord injury in the cervical spine, and were enrolled in the trial if a diagnosis had been made and treatment had begun within 8 hours. Complications of high-dose therapy with MPSS were compared with placebo treatment throughout the study period and up to 2 months after injury. RESULTS: The MPSS group had 13 patients (56.5%) with complications, whereas the placebo group had 8 (34.8%). The difference between the two groups was not statistically significant ($P = 0.139$). There were eight instances of pulmonary complication with MPSS (34.8%) and one instance (4.34%) with placebo ($P = 0.009$). There were four instances of gastrointestinal complication (17.4%) with MPSS and none with placebo ($P = 0.036$). Pulmonary complications were more prevalent in patients aged more than 60 years ($P = 0.029$). CONCLUSION: Aged patients with cervical spinal injury may be more likely to have pulmonary side effects ($P = 0.029$) after high-dose therapy with MPSS and thus deserve special care.

Holinka CF. Design and conduct of clinical trials in hormone replacement therapy. *Ann N Y Acad Sci* 2001 Sep;943:89-108

Postmenopausal hormone replacement therapy represents an area of outstanding importance in preventive medicine that greatly affects personal well-being as well as public health. The number of women living in the United States who are 50 years or older has been estimated at nearly 50 million. Many of those women are likely to be eligible for postmenopausal hormone replacement, which may consist either of estrogen replacement therapy (ERT) in women without a uterus or, more frequently, estrogen/progestin combination therapy (HRT) in women with a uterus. This chapter first presents an overview of general regulatory requirements pertaining to the design and conduct of clinical studies in support of marketing approval for a drug product. These requirements include, but are not restricted to, studies in HRT. The chapter next discusses the design and conduct of clinical trials in support of marketing approval for the indications: treatment of moderate to severe vasomotor symptoms and vulvovaginal atrophy; prevention of osteoporosis; and protection by adjunctive progestin against estrogen-induced endometrial hyperplasia/cancer in women with a uterus. Finally, data related to the potential cardioprotective action of HRT and its protection against Alzheimer's disease and colon cancer are discussed.

Burkman RT, Collins JA, Greene RA. Current perspectives on benefits and risks of hormone replacement therapy. *Am J Obstet Gynecol* 2001 Aug;185(2 Suppl):S13-23 .

Hormone replacement therapy with estrogen alone or with added progestin relieves menopausal symptoms and physical changes associated with depleted endogenous estrogen levels.

5 Estrogen replacement has also demonstrated a clear benefit in the prevention of osteoporosis. Hormone replacement therapy with added progestin maintains spinal bone density, protects against postmenopausal hip fractures, and provides these benefits even when therapy is started after age 60. More recently, additional benefits have emerged. Current estrogen and hormone replacement therapy users have a 34% reduction in the risk of colorectal cancer and a 20% to 60%
10 reduction in the risk of Alzheimer's disease. Until recently, the body of evidence indicated that hormone replacement therapy with estrogen only reduced cardiovascular disease risk by 40% to 50% in healthy patients; whether the findings of 3 ongoing trials will change this conclusion is pending availability of the final results. The many benefits of estrogen and hormone replacement therapy must be weighed against a slight increase in the risk of breast cancer diagnosis with use
15 for 5 or more years, but which disappears following cessation of therapy. Overall, estrogen and hormone replacement therapy improves the quality of life and increases life expectancy for most menopausal women.

Gaillard PJ, van Der Meide PH, de Boer AG, Breimer DD. Glucocorticoid and type 1 interferon interactions at the blood-brain barrier: relevance for drug therapies for multiple
20 sclerosis. *Neuroreport* 2001 Jul 20;12(10):2189-93.

The pharmacological effect of glucocorticoids and type 1 interferons (IFNs), simultaneously used as therapeutics for multiple sclerosis (MS), on the (inflamed) blood-brain barrier (BBB) was investigated in vitro. Although both drugs additively decreased BBB permeability, they did not prevent the increase in BBB permeability induced by
25 lipopolysaccharide (LPS), which served as a pro-inflammatory stimulus. The beneficial clinical effect of glucocorticoid and IFN therapy for MS seems therefore not to be mediated through a direct action at the level of the BBB. Most strikingly, however, pretreatment with type 1 IFNs (alpha and beta) potentiated the effect of glucocorticoids by two orders of magnitude. This lead us

to hypothesize that type 1 IFNs may restore the dysfunctional T-helper 1 (Th1)/Th2 balance associated with MS, by a mechanism that involves an increased sensitivity for glucocorticoids.

Panel 2D Summary: Ag2248/Ag2548

The expression of the CG50307-01 gene shows good concordance between two independent runs. The highest level of expression was seen in a breast cancer sample (CTs=27-29). In addition, this gene appears to be overexpressed in ovarian, gastric, breast, uterine, lung and colon cancers relative to the normal adjacent tissues from these patients. Therefore, the expression of this gene could be of use as a diagnostic marker for the presence of these cancers. Furthermore, therapeutic inhibition of the activity of this gene product may be effective in the treatment of these cancers.

Panel 3D Summary: Ag2548

The CG50307-01 gene is expressed at a low to moderate level in most of the cells and tissues used in this panel, with highest expression in the small cell lung cancer cell line DMS-79 (CT=27.79). This ubiquitous expression suggests that the gene product plays a role in cell survival and proliferation for a majority of cell types except cell lines derived from tongue squamous cell carcinoma.

Panel 4D Summary: Ag2248

The CG50307-01 gene encodes a steroid dehydrogenase-like protein and is expressed at moderate levels (CT=28-32) in numerous immune cell types and tissues. Small molecule antagonists that block the function of the steroid dehydrogenase-like protein encoded by this gene may be useful as therapeutics that reduce or eliminate the symptoms of patients suffering from autoimmune and inflammatory diseases such as asthma, allergies, inflammatory bowel disease, lupus erythematosus, or rheumatoid arthritis. Please note that data from a second run using the probe and primer set Ag2548 is not included. The amp plot suggests that there were experimental difficulties with this run.

Panel 5 Islet Summary: Ag2248

The expression of this novel steroid dehydrogenase-like gene, CG50307-01, is highest in the liver HepG2 cell line, (CT=32.1). Lower but still significant levels of expression are seen in several placenta samples, uterine smooth muscle, adipose samples, differentiated mesenchymal stem cells, kidney and skeletal muscle from a diabetic patient. Expression in liver cells and placenta suggests that the role of this novel steroid dehydrogenase may be similar to the role of other steroid dehydrogenases which are involved in steroid and bile acid metabolism. Very low expression of this gene is also seen in a human pancreatic islet sample. Therefore, small molecule therapeutics against this gene product may be effective in disorders in which expression of this gene is dysregulated.

Panel 5D Summary: Ag2248

The expression of the CG50307-01 gene is generally similar to that in panel 5I, although the relative abundances in each of the tissues are different. This panel shows highest expression of this steroid dehydrogenase-like gene in placenta from a diabetic patient (CT=32.2), with lower expression in other placenta samples. Relative expression of this gene is also high in the skeletal muscle of a diabetic patient and in liver HepG2 cells. Low but significant levels of expression are also seen in some adipose samples and in differentiated mesenchymal stem cells, in kidney and in uterus. Expression in liver cells and placenta suggests that the role of this novel steroid dehydrogenase may be similar to the role of other steroid dehydrogenases which are involved in steroid and bile acid metabolism. Small molecule therapeutics against this gene product may be effective in disorders in which expression of this gene is dysregulated.

Panel CNS_1 Summary: Ag2248

This panel confirms expression of the CG50307-01 gene in the brain. Please see Panel 1.3D for discussion of potential utility in the central nervous system.

NOV11 (CG50311-01: Novel nonmuscle myosin)

Expression of gene CG50311-01 was assessed using the primer-probe set Ag2546, described in Table LA. Results of the RTQ-PCR runs are shown in Tables LB, LC and LD.

Table LA. Probe Name Ag2546

Primers	Sequences	Length	Start Position
Forward	5'-gttctgtgtggtcatcaatcct-3' (SEQ ID NO:181)	22	487
Probe	TET-5'-caagaacctgccatctactctgaaga-3'-TAMRA (SEQ ID NO:182)	27	511
Reverse	5'-cttgcccttgtagattttcca-3' (SEQ ID NO:183)	20	543

Table LB. Panel 1.3D

Tissue Name	Rel. Exp.(%) Ag2546, Run 165532775	Tissue Name	Rel. Exp.(%) Ag2546, Run 165532775
Liver adenocarcinoma	15.4	Kidney (fetal)	9.0
Pancreas	4.0	Renal ca. 786-0	44.1
Pancreatic ca. CAPAN 2	9.3	Renal ca. A498	38.2
Adrenal gland	3.8	Renal ca. RXF 393	41.5
Thyroid	5.2	Renal ca. ACHN	20.9
Salivary gland	6.7	Renal ca. UO-31	63.7
Pituitary gland	1.4	Renal ca. TK-10	8.7
Brain (fetal)	2.6	Liver	1.5
Brain (whole)	6.8	Liver (fetal)	6.1
Brain (amygdala)	6.4	Liver ca. (hepatoblast) HepG2	15.4
Brain (cerebellum)	4.5	Lung	19.8
Brain (hippocampus)	4.6	Lung (fetal)	9.5
Brain (substantia nigra)	3.2	Lung ca. (small cell) LX-1	10.7
Brain (thalamus)	3.7	Lung ca. (small cell) NCI-H69	14.6
Cerebral Cortex	5.1	Lung ca. (s.cell var.) SHP-77	19.8
Spinal cord	5.8	Lung ca. (large cell) NCI-H460	11.1
glio/astro U87-MG	15.9	Lung ca. (non-sm. cell) A549	3.8
glio/astro U-118-MG	100.0	Lung ca. (non-s.cell) NCI-H23	2.4
astrocytoma SW1783	54.7	Lung ca. (non-s.cell) HOP-62	29.7

neuro*; met SK-N-AS	2.7	Lung ca. (non-s.cl) NCI-H522	1.6
astrocytoma SF-539	27.9	Lung ca. (squam.) SW 900	17.8
astrocytoma SNB-75	60.3	Lung ca. (squam.) NCI-H596	10.7
glioma SNB-19	16.3	Mammary gland	12.2
glioma U251	54.0	Breast ca.* (pl.ef) MCF-7	7.1
glioma SF-295	28.5	Breast ca.* (pl.ef) MDA-MB-231	64.2
Heart (Fetal)	4.0	Breast ca.* (pl. ef) T47D	4.2
Heart	9.3	Breast ca. BT-549	52.5
Skeletal muscle (Fetal)	5.3	Breast ca. MDA-N	0.8
Skeletal muscle	6.8	Ovary	14.4
Bone marrow	8.2	Ovarian ca. OVCAR- 3	11.1
Thymus	7.7	Ovarian ca. OVCAR- 4	19.9
Spleen	12.2	Ovarian ca. OVCAR- 5	17.0
Lymph node	28.3	Ovarian ca. OVCAR- 8	4.9
Colorectal	13.1	Ovarian ca. IGROV-1	2.8
Stomach	9.3	Ovarian ca. (ascites) SK-OV-3	31.2
Small intestine	11.5	Uterus	40.6
Colon ca. SW480	8.1	Placenta	9.5
Colon ca.* SW620 (SW480 met)	7.4	Prostate	3.2
Colon ca. HT29	3.6	Prostate ca.* (bone met) PC-3	7.0
Colon ca. HCT-116	6.9	Testis	2.8
Colon ca. CaCo-2	9.0	Melanoma Hs688(A).T	22.4
CC Well to Mod Diff (ODO3866)	29.3	Melanoma* (met) Hs688(B).T	27.2
Colon ca. HCC-2998	6.8	Melanoma UACC-62	7.1
Gastric ca. (liver met) NCI-N87	15.1	Melanoma M14	51.4

Bladder	21.9	Melanoma LOX IMVI	4.5
Trachea	8.5	Melanoma* (met) SK-MEL-5	6.6
Kidney	5.8	Adipose	14.3

Table LC. Panel 2.2

Tissue Name	Rel. Exp.(%) Ag2546, Run 174575196	Tissue Name	Rel. Exp.(%) Ag2546, Run 174575196
Normal Colon	33.4	Kidney Margin (OD04348)	100.0
Colon cancer (OD06064)	60.7	Kidney malignant cancer (OD06204B)	7.9
Colon Margin (OD06064)	29.1	Kidney normal adjacent tissue (OD06204E)	10.4
Colon cancer (OD06159)	5.7	Kidney Cancer (OD04450-01)	34.4
Colon Margin (OD06159)	34.6	Kidney Margin (OD04450-03)	24.8
Colon cancer (OD06297- 04)	11.7	Kidney Cancer 8120613	1.0
Colon Margin (OD06297-015)	39.5	Kidney Margin 8120614	19.9
CC Gr.2 ascend colon (ODO3921)	6.3	Kidney Cancer 9010320	6.4
CC Margin (ODO3921)	7.2	Kidney Margin 9010321	11.1
Colon cancer metastasis (OD06104)	3.0	Kidney Cancer 8120607	35.6
Lung Margin (OD06104)	16.0	Kidney Margin 8120608	10.9
Colon mets to lung (OD04451-01)	35.6	Normal Uterus	90.8
Lung Margin (OD04451- 02)	53.6	Uterine Cancer 064011	7.6
Normal Prostate	6.4	Normal Thyroid	1.1
Prostate Cancer (OD04410)	1.8	Thyroid Cancer	6.7
Prostate Margin (OD04410)	4.0	Thyroid Cancer A302152	11.5
Normal Ovary	35.8	Thyroid Margin A302153	3.8

Ovarian cancer (OD06283-03)	18.6	Normal Breast	61.6
Ovarian Margin (OD06283-07)	30.4	Breast Cancer	7.6
Ovarian Cancer	11.9	Breast Cancer	40.3
Ovarian cancer (OD06145)	4.4	Breast Cancer (OD04590-01)	27.9
Ovarian Margin (OD06145)	22.1	Breast Cancer Mets (OD04590-03)	31.4
Ovarian cancer (OD06455-03)	14.0	Breast Cancer Metastasis	26.4
Ovarian Margin (OD06455-07)	15.3	Breast Cancer	33.4
Normal Lung	19.3	Breast Cancer 9100266	15.9
Invasive poor diff. lung adeno (ODO4945-01)	14.1	Breast Margin 9100265	30.4
Lung Margin (ODO4945-03)	33.9	Breast Cancer A209073	9.2
Lung Malignant Cancer (OD03126)	18.6	Breast Margin A2090734	28.5
Lung Margin (OD03126)	6.5	Breast cancer (OD06083)	48.0
Lung Cancer (OD05014A)	21.5	Breast cancer node metastasis (OD06083)	35.6
Lung Margin (OD05014B)	44.8	Normal Liver	15.8
Lung cancer (OD06081)	8.4	Liver Cancer 1026	16.2
Lung Margin (OD06081)	19.8	Liver Cancer 1025	33.2
Lung Cancer (OD04237-01)	4.3	Liver Cancer 6004-T	19.6
Lung Margin (OD04237-02)	58.6	Liver Tissue 6004-N	4.9
Ocular Mel Met to Liver (ODO4310)	9.7	Liver Cancer 6005-T	44.8
Liver Margin (ODO4310)	9.0	Liver Tissue 6005-N	64.6
Melanoma Metastasis	3.4	Liver Cancer	29.5
Lung Margin (OD04321)	36.6	Normal Bladder	15.1
Normal Kidney	5.3	Bladder Cancer	15.7
Kidney Ca, Nuclear grade 2 (OD04338)	46.7	Bladder Cancer	21.2

Kidney Margin (OD04338)	4.6	Normal Stomach	54.3
Kidney Ca Nuclear grade 1/2 (OD04339)	26.6	Gastric Cancer 9060397	6.4
Kidney Margin (OD04339)	15.5	Stomach Margin 9060396	22.4
Kidney Ca, Clear cell type (OD04340)	17.0	Gastric Cancer 9060395	19.3
Kidney Margin (OD04340)	20.3	Stomach Margin 9060394	35.1
Kidney Ca, Nuclear grade 3 (OD04348)	15.3	Gastric Cancer 064005	11.4

Table LD. Panel 4D

Tissue Name	Rel. Exp.(%) Ag2546, Run 164321138	Tissue Name	Rel. Exp.(%) Ag2546, Run 164321138
Secondary Th1 act	34.2	HUVEC IL-1beta	26.6
Secondary Th2 act	33.7	HUVEC IFN gamma	45.7
Secondary Tr1 act	34.4	HUVEC TNF alpha + IFN gamma	58.6
Secondary Th1 rest	15.7	HUVEC TNF alpha + IL4	58.6
Secondary Th2 rest	28.5	HUVEC IL-11	28.5
Secondary Tr1 rest	26.8	Lung Microvascular EC none	60.7
Primary Th1 act	30.8	Lung Microvascular EC TNFalpha + IL-1beta	64.6
Primary Th2 act	36.9	Microvascular Dermal EC none	66.9
Primary Tr1 act	40.9	Microvascular Dermal EC TNFalpha + IL-1beta	61.1
Primary Th1 rest	75.8	Bronchial epithelium TNFalpha + IL1beta	66.9
Primary Th2 rest	60.3	Small airway epithelium none	32.8
Primary Tr1 rest	49.7	Small airway epithelium TNFalpha + IL-1beta	95.3
CD45RA CD4 lymphocyte act	42.0	Coronary artery SMC rest	61.1
CD45RO CD4 lymphocyte act	39.0	Coronary artery SMC TNFalpha + IL-1beta	36.6

CD8 lymphocyte act	35.6	Astrocytes rest	66.0
Secondary CD8 lymphocyte rest	41.2	Astrocytes TNFalpha + IL-1beta	46.0
Secondary CD8 lymphocyte act	26.1	KU-812 (Basophil) rest	7.6
CD4 lymphocyte none	22.2	KU-812 (Basophil) PMA/ionomycin	29.5
2ry Th1/Th2/Tr1_anti-CD95 CH11	38.4	CCD1106 (Keratinocytes) none	56.6
LAK cells rest	30.8	CCD1106 (Keratinocytes) TNFalpha + IL-1beta	57.0
LAK cells IL-2	43.8	Liver cirrhosis	9.8
LAK cells IL-2+IL-12	37.6	Lupus kidney	6.5
LAK cells IL-2+IFN gamma	41.2	NCI-H292 none	17.7
LAK cells IL-2+ IL-18	38.2	NCI-H292 IL-4	26.2
LAK cells PMA/ionomycin	38.4	NCI-H292 IL-9	26.6
NK Cells IL-2 rest	30.4	NCI-H292 IL-13	19.6
Two Way MLR 3 day	27.2	NCI-H292 IFN gamma	19.2
Two Way MLR 5 day	21.9	HPAEC none	46.0
Two Way MLR 7 day	26.2	HPAEC TNF alpha + IL-1 beta	54.0
PBMC rest	27.5	Lung fibroblast none	46.7
PBMC PWM	71.2	Lung fibroblast TNF alpha + IL-1 beta	28.7
PBMC PHA-L	44.8	Lung fibroblast IL-4	77.4
Ramos (B cell) none	23.7	Lung fibroblast IL-9	68.3
Ramos (B cell) ionomycin	59.9	Lung fibroblast IL-13	62.0
B lymphocytes PWM	66.9	Lung fibroblast IFN gamma	81.2
B lymphocytes CD40L and IL-4	47.6	Dermal fibroblast CCD1070 rest	77.4
EOL-1 dbcAMP	20.3	Dermal fibroblast CCD1070 TNF alpha	100.0
EOL-1 dbcAMP PMA/ionomycin	25.9	Dermal fibroblast CCD1070 IL-1 beta	54.0
Dendritic cells none	23.0	Dermal fibroblast IFN gamma	18.2
Dendritic cells LPS	25.5	Dermal fibroblast IL-4	27.2
Dendritic cells anti-	26.2	IBD Colitis 2	2.4

CD40			
Monocytes rest	31.6	IBD Crohn's	2.4
Monocytes LPS	17.7	Colon	22.4
Macrophages rest	33.0	Lung	45.4
Macrophages LPS	20.9	Thymus	28.5
HUVEC none	49.0	Kidney	39.5
HUVEC starved	85.9		

Panel 1.3D Summary: Ag2546

The CG50311-01 gene is expressed at moderate levels in all cell lines and tissues in this panel, with highest expression in a glioblastoma/ astrocytoma cell line (CT=25.3). There is slightly increased expression in renal and brain cancer cell lines compared to normal tissues
5 suggesting a possible role in these cancers.

This gene is also expressed at moderate levels in all endocrine (metabolic)-related regions examined. Therefore, therapeutic modulation of this gene or its protein product may be of use in the treatment of any endocrine (metabolic)-related disease where neuronal feedback is critical.

This gene encodes a myosin homolog that is expressed at moderate levels in all brain
10 regions examined. Nonmuscle myosin is believed to be involved in the migration of neural growth cones. Therefore, therapeutic modulation of this gene or its protein product may be of use in the treatment of any CNS disease that involves neuronal death/ neurodegeneration (Alzheimer's, Parkinson's, Huntington's diseases, stroke, brain or spinal cord trauma) and may also aid in compensatory synaptogenesis.

15 References:

Kira M, Tanaka J, Sobue K. Caldesmon and low Mr isoform of tropomyosin are localized in neuronal growth cones. J Neurosci Res 1995 Feb 15;40(3):294-305.

Neuronal growth cones move actively, accompanying changes in intracellular Ca²⁺ concentration. The movement of growth cones may partly depend on the actomyosin system,
20 considering the presence of actin and myosin II. Yet, Ca(2+)-sensitive regulatory proteins for the actomyosin system have not been identified in growth cones. In the present study, caldesmon, an

inhibitory protein on actin-myosin interaction, was detected in the growth cone fraction isolated from embryonic rat brain, using immunoblotting with the antibody to chicken gizzard caldesmon. Morphological evidence of caldesmon in growth cones of cultured rat neurons was obtained using the indirect immunofluorescence method. Since inhibition of caldesmon on actin-myosin
5 interaction can be overcome by calmodulin and Ca^{2+} , caldesmon may be involved in the Ca^{2+} -dependent regulation in growth cone motility. Tropomyosin is another member of the actomyosin system whose function may be regulated by caldesmon in smooth and nonmuscle cells. A low Mr isoform of tropomyosin was distributed in the growth cone fraction. Using specific antibodies against tropomyosin isoforms, we further clarified morphologically that the low Mr isoform was
10 localized in growth cones, but not the high Mr isoform. High Mr isoforms of tropomyosin were present in nonneuronal cells. Actin filaments in growth cones may be unstable, since low Mr tropomyosin binds to actin filaments with a lower affinity than high Mr isoforms. The instability of actin filaments may be suitable for the rapid movement and shape changes of growth cones.

Panel 2.2 Summary: Ag2546

15 The CG50311-01 gene is expressed at moderate levels in all the samples on this panel with slightly higher expression in normal lung, breast and stomach tissue compared to the adjacent tumor tissue. Hence, expression of this gene might be used as a marker to identify normal tissue from cancerous tissue in these organs.

Panel 4D Summary: Ag2546

20 The CG50311-01 gene is expressed at high levels ($\text{CTs} = 24.9\text{-}27.4$) in a wide range of cell types with significant importance in innate and specific immunity and also other cell types associated with inflammatory diseases. The highest expression of this transcript is found in dermal and lung fibroblasts treated with cytokines, and in small airway epithelium and HUVEC. Therefore, inhibition of the function of the protein
25 encoded by this gene through the application of a small molecule drug may reduce or eliminate the symptoms associated with T cell, B cell, endothelial and fibroblast activity such as those found in chronic obstructive pulmonary disease, asthma, emphysema, psoriasis, inflammatory bowel disease, rheumatoid arthritis, osteoarthritis and lupus erythematosus.

NOV12a (CG50323-01: Pancreatitis-associated protein)

Expression of gene CG50323-01 was assessed using the primer-probe set Ag3760, described in Table IA.

5 Table IA. Probe Name Ag3760

Primers	Sequences	Length	Start Position
Forward	5'-caattgcctccagtatttgaac-3' (SEQ ID NO:184)	22	506
Probe	TET-5'-ttgcagacatagggtaacctcacatt-3'-TAMRA (SEQ ID NO:185)	26	480
Reverse	5'-agcatttctgaggtggaaaga-3' (SEQ ID NO:186)	21	449

CNS_neurodegeneration_v1.0 Summary: Ag3760

Expression of the CG50323-01 gene is low/undetectable in all samples on this panel (CT>35).

General_screening_panel_v1.4 Summary: Ag3760

10 Expression of the CG50323-01 gene is low/undetectable in all samples on this panel (CT>35).

Panel 4.1D Summary: Ag3760

Expression of the CG50323-01 gene is low/undetectable in all samples on this panel (CT>35).

15

Example 2. Identification of NOVX clones

20 The novel NOVX target sequences identified in the present invention were subjected to the exon linking process to confirm the sequence. PCR primers were designed by starting at the most upstream sequence available, for the forward primer, and at the most downstream sequence available for the reverse primer. Table M1 shows the sequences of the PCR primers used for obtaining different clones. In each case, the sequence was examined, walking inward from the

respective termini toward the coding sequence, until a suitable sequence that is either unique or highly selective was encountered, or, in the case of the reverse primer, until the stop codon was reached. Such primers were designed based on *in silico* predictions for the full length cDNA, part (one or more exons) of the DNA or protein sequence of the target sequence, or by translated

5 homology of the predicted exons to closely related human sequences from other species. These primers were then employed in PCR amplification based on the following pool of human cDNAs: adrenal gland, bone marrow, brain - amygdala, brain - cerebellum, brain - hippocampus, brain - substantia nigra, brain - thalamus, brain -whole, fetal brain, fetal kidney, fetal liver, fetal lung, heart, kidney, lymphoma - Raji, mammary gland, pancreas, pituitary gland, placenta, prostate,

10 salivary gland, skeletal muscle, small intestine, spinal cord, spleen, stomach, testis, thyroid, trachea, uterus.

Table M1

NOVX Clone	Forward Primer	Reverse Primer
NOV1c- NOV1j	GGATCCAGAATTCTGCAAAATCTTACGACTTTGG (SEQ ID NO:187)	CGGCCGATAGCAGAAGACATCCCACATTTCACTCTTG (SEQ ID NO:188)
NOV3b	TGCGCGCTCGTCGTCCTC (SEQ ID NO:189)	GGAGGCCACAGGAGCAGGATCA (SEQ ID NO:190)
NOV5b	AGATCTCTGGGCGCAACGGTCATCTGTAACAAGATCC (SEQ ID NO:191)	CTCGAGCTTGCACGTGTACATCTCCGTGCGCTCG (SEQ ID NO:192)
NOV6b	GGATCCAGCCCTGGCCAGGCCGTGTGCAACTTCG (SEQ ID NO:193)	CTCGAGTGTGTTCCCCGGGCTGGGGGCAGGCTGC (SEQ ID NO:194)
NOV7b and NOV7c	ATGTCTGTGGCCATGGTAGAGTCAGG (SEQ ID NO:195)	ATCATGAACCTCAACTCCTCAGGAACC (SEQ ID NO:196)
NOV8	CAAGAGCAGGTTTGAGATGTTCTC (SEQ ID NO:197)	CCAAGGTTGACCACCTCCAT (SEQ ID NO:198)
NOV10b	ATCTACGGAGTCCCTTTGGCCACATAA (SEQ ID NO:199)	TCCAAATGTCAGAATATCGAGGTTCCC (SEQ ID NO:200)
NOV11	CCGCCTGTGTTCCATGGCTT (SEQ ID NO:201)	GTCATTCTGCTGCCGGTTGGTAG (SEQ ID NO:202)
NOV12a	CCATGGCCCTGCCAAGTGTATCTT (SEQ ID NO:203)	TTACAATTGCCTCCAGTATTTGAACTTGCA (SEQ ID NO:204)
NOV12b and NOV12c	AAGCTTGAAGAACCCAGAGGGAAGTGCCTCTGC (SEQ ID NO:205)	CTCGAGCAATTGCCTCCAGTATTTGAACTTGC (SEQ ID NO:206)

15 Usually the resulting amplicons were gel purified, cloned and sequenced to high redundancy. The PCR product derived from exon linking was cloned into the pCR2.1 vector from Invitrogen. The resulting bacterial clone has an insert covering the entire open reading frame

cloned into the pCR2.1 vector. Table M2 shows a list of these bacterial clones. The resulting sequences from all clones were assembled with themselves, with other fragments in CuraGen Corporation's database and with public ESTs. Fragments and ESTs were included as components for an assembly when the extent of their identity with another component of the assembly was at least 95% over 50 bp. In addition, sequence traces were evaluated manually and edited for corrections if appropriate. These procedures provide the sequence reported herein.

Table M2	
NOVX Clone	Bacterial Clone (Physical clone)
NOV3a	124906::133267070.698458.L7
NOV8	SC87760822_A.698299.L11
NOV10b	124893::CG50307-01.698453.H17

Real time quantitative PCR

Relative expression levels of the mRNA of the invention across a panel of 92 human samples was determined by real-time quantitative PCR analysis. These samples represent multiple tissue types, normal and diseased states, physiological states, and developmental states from different donors. Samples were obtained as whole tissue, cell lines, primary cells or tissue cultured primary cells and cell lines. Cells and cell lines may have been treated with biological or chemical agents that regulate gene expression for example, growth factors, chemokines, steroids.

Table M3 shows the primers/probe used for this reaction. The primers and probe were designed to specifically identify the gene of the invention irrespective of the presence of related human genes like splice forms, homologs and paralogs.

Table M3			
NOVX Clone	Forward Primer	Reverse Primer	Probe
NOV8	GCACTTGAAGAGCTGTCATAGC (SEQ ID NO:207)	TACCCTGAGTCTCTTGATTCCA (SEQ ID NO:208)	TET-5' - CTCTATGACTGCCAGCAAATCACACG- 3' -TAMRA (SEQ ID NO:209)

Example 3. SNP analysis of NOVX clones

SeqCalling™ Technology: cDNA was derived from various human samples representing multiple tissue types, normal and diseased states, physiological states, and developmental states from different donors. Samples were obtained as whole tissue, cell lines, primary cells or tissue cultured primary cells and cell lines. Cells and cell lines may have been treated with biological or chemical agents that regulate gene expression for example, growth factors, chemokines, steroids. The cDNA thus derived was then sequenced using CuraGen's proprietary SeqCalling technology. Sequence traces were evaluated manually and edited for corrections if appropriate. cDNA sequences from all samples were assembled with themselves and with public ESTs using bioinformatics programs to generate CuraGen's human SeqCalling database of SeqCalling assemblies. Each assembly contains one or more overlapping cDNA sequences derived from one or more human samples. Fragments and ESTs were included as components for an assembly when the extent of identity with another component of the assembly was at least 95% over 50-bp. Each assembly can represent a gene and/or its variants such as splice forms and/or single nucleotide polymorphisms (SNPs) and their combinations.

Variant sequences are included in this application. A variant sequence can include a single nucleotide polymorphism (SNP). A SNP can, in some instances, be referred to as a "cSNP" to denote that the nucleotide sequence containing the SNP originates as a cDNA. A SNP can arise in several ways. For example, a SNP may be due to a substitution of one nucleotide for another at the polymorphic site. Such a substitution can be either a transition or a transversion. A SNP can also arise from a deletion of a nucleotide or an insertion of a nucleotide, relative to a reference allele. In this case, the polymorphic site is a site at which one allele bears a gap with respect to a particular nucleotide in another allele. SNPs occurring within genes may result in an alteration of the amino acid encoded by the gene at the position of the SNP. Intragenic SNPs may also be silent, however, in the case that a codon including a SNP encodes the same amino acid as a result of the redundancy of the genetic code. SNPs occurring outside the region of a gene, or in an intron within a gene, do not result in changes in any amino acid sequence of a protein but may result in altered regulation of the expression pattern for example, alteration in temporal expression, physiological response regulation, cell type expression regulation, intensity of expression, stability of transcribed message.

Method of novel SNP Identification: SNPs are identified by analyzing sequence assemblies using CuraGen's proprietary SNPTool algorithm. SNPTool identifies variation in assemblies with the following criteria: SNPs are not analyzed within 10 base pairs on both ends of an alignment; Window size (number of bases in a view) is 10; The allowed number of mismatches in a window is 2; Minimum SNP base quality (PHRED score) is 23; Minimum number of changes to score an SNP is 2/assembly position. SNPTool analyzes the assembly and displays SNP positions, associated individual variant sequences in the assembly, the depth of the assembly at that given position, the putative assembly allele frequency, and the SNP sequence variation. Sequence traces are then selected and brought into view for manual validation. The consensus assembly sequence is imported into CuraTools along with variant sequence changes to identify potential amino acid changes resulting from the SNP sequence variation. Comprehensive SNP data analysis is then exported into the SNPCalling database.

Method of novel SNP Confirmation:

SNPs are confirmed employing a validated method known as Pyrosequencing (Pyrosequencing, Westborough, MA). Detailed protocols for Pyrosequencing can be found in: Alderborn et al. Determination of Single Nucleotide Polymorphisms by Real-time Pyrophosphate DNA Sequencing. (2000). *Genome Research*. 10, Issue 8, August. 1249-1265. In brief, Pyrosequencing is a real time primer extension process of genotyping. This protocol takes double-stranded, biotinylated PCR products from genomic DNA samples and binds them to streptavidin beads. These beads are then denatured producing single stranded bound DNA. SNPs are characterized utilizing a technique based on an indirect bioluminometric assay of pyrophosphate (PPi) that is released from each dNTP upon DNA chain elongation. Following Klenow polymerase-mediated base incorporation, PPi is released and used as a substrate, together with adenosine 5'-phosphosulfate (APS), for ATP sulfurylase, which results in the formation of ATP. Subsequently, the ATP accomplishes the conversion of luciferin to its oxi-derivative by the action of luciferase. The ensuing light output becomes proportional to the number of added bases, up to about four bases. To allow processivity of the method dNTP excess is degraded by apyrase, which is also present in the starting reaction mixture, so that only dNTPs are added to the template during the sequencing. The process has been fully automated and adapted to a 96-well format, which allows rapid screening of large SNP panels. The DNA and protein sequences for the novel

single nucleotide polymorphic variants are reported. Variants are reported individually but any combination of all or a select subset of variants are also included. In addition, the positions of the variant bases and the variant amino acid residues are underlined.

RESULTS

5 Variants are reported individually but any combination of all or a select subset of variants are also included as contemplated NOVX embodiments of the invention.

NOV1a SNP data

10 The DNA and protein sequences for the novel single nucleotide polymorphic variants of the Stablin-like gene of NOV1a are reported in Table N1. Variants are reported individually but any combination of all or a select subset of variants are also included. In summary, there are 5 variants reported.

Table N1. cSNP and Coding Variants for NOV1a				
Variant	Base Position of cSNP	Wild Type	Variant	Amino Acid Change
13376228	4185	T	C	silent (no change)
13376229	4524	T	C	silent
13376230	4654	G	A	Gly → Ser at aa 1552
13376231	4671	A	G	silent
13376232	4820	T	C	Leu → Pro at aa 1607

NOV2a SNP data

15 The DNA and protein sequences for the novel single nucleotide polymorphic variants of the Polydom-like gene of NOV2a are reported in Table N2. Variants are reported individually but any combination of all or a select subset of variants are also included. In summary, there are 10 variants reported.

Table N2. cSNP and Coding Variants for NOV2a				
Variant	Base Position of cSNP	Wild Type	Variant	Amino Acid Change
13374700	717	A	G	Glu → Gly at aa 214

13374701	2303	A	G	Asn → Asp at aa 743
13374256	7348	T	C	silent
13376233	7370	C	T	Pro → ser at aa 2432
13376234	8665	G	A	silent
13376235	8827	C	T	silent
13376236	9018	A	G	His → Arg at aa 2981
13376237	9551	A	G	Thr → Ala at aa 3159
13376238	9790	T	G	silent
13376239	10025	G	T	Gly → End at aa 3317

NOV3a SNP data

The DNA and protein sequences for the novel single nucleotide polymorphic variants of the Transmembrane-like gene of NOV3a are reported in Table N3. Variants are reported individually but any combination of all or a select subset of variants are also included. In summary, there are 4 variants reported.

Table N3. cSNP and Coding Variants for NOV3a

Variant	Base Position of cSNP	Wild Type	Variant	Amino Acid Change
13376243	145	A	G	Ile → Val at aa 49
13376242	336	G	A	Trp → End at aa 112
13376241	494	G	A	Gly → Asp at aa 165
13376240	495	C	T	silent

NOV4 SNP data

The DNA and protein sequences for the novel single nucleotide polymorphic variants of the Serine Protease-like gene of NOV4 are reported in Table N4. Variants are reported

individually but any combination of all or a select subset of variants are also included. In summary, there are 3 variants reported.

Table N4. cSNP and Coding Variants for NOV4				
Variant	Base Position of cSNP	Wild Type	Variant	Amino Acid Change
13376246	122	G	A	Val → Ile at aa 37
13376245	258	A	G	His → Arg at aa 82
13376244	296	C	T	Arg → Cys at aa 95

NOV5a SNP data

- 5 The DNA and protein sequences for the novel single nucleotide polymorphic variants of the Wnt7a-like gene of NOV5a are reported in Table N5. Variants are reported individually but any combination of all or a select subset of variants are also included. In summary, there are 2 variants reported.

Table N5. cSNP and Coding Variants for NOV5a				
Variant	Base Position of cSNP	Wild Type	Variant	Amino Acid Change
13376247	315	G	A	silent
13376248	459	T	C	silent

10 NOV6a SNP data

- The DNA and protein sequences for the novel single nucleotide polymorphic variants of the Apical Endosomal Glycoprotein-like gene of NOV6a are reported in Table N6. Variants are reported individually but any combination of all or a select subset of variants are also included. In
15 summary, there is 1 variant reported.

Table N6. cSNP and Coding Variants for NOV6a

Variant	Base Position of cSNP	Wild Type	Variant	Amino Acid Change
13376249	3477	C	T	Pro → Ser at aa 1147

NOV7a SNP data

The DNA and protein sequences for the novel single nucleotide polymorphic variants of the ADAM13-like gene of NOV7a are reported in Table N7. Variants are reported individually but any combination of all or a select subset of variants are also included. In summary, there are 2 variants reported.

Table N7. cSNP and Coding Variants for NOV7a

Variant	Base Position of cSNP	Wild Type	Variant	Amino Acid Change
13374267	2130	G	A	Val → Ile at aa 710
13374266	2153	G	C	silent

NOV8 SNP data

The DNA and protein sequences for the novel single nucleotide polymorphic variants of the Leucine Rich Containing F-Box Protein-like gene of NOV8 are reported in Table N8. Variants are reported individually but any combination of all or a select subset of variants are also included. In summary, there are 2 variants reported.

Table N8. cSNP and Coding Variants for NOV8a

Variant	Base Position of cSNP	Wild Type	Variant	Amino Acid Change
13373958	366	T	C	Ile → Thr at aa 117
13373959	452	C	T	Pro → Ser at aa 146

NOV10a SNP data

The DNA and protein sequences for the novel single nucleotide polymorphic variants of the Steroid dehydrogenase-like gene of NOV10a are reported in Table N9. Variants are reported

individually but any combination of all or a select subset of variants are also included. In summary, there are 2 variants reported.

Table N9. cSNP and Coding Variants for NOV10a

Variant	Base Position of cSNP	Wild Type	Variant	Amino Acid Change
13375812	465	A	G	Ile → Val at aa 95
13375811	1162	C	G	Ser → Cys at aa 327

5

NOV11 SNP data

The DNA and protein sequences for the novel single nucleotide polymorphic variants of the Myosin Heavy Chain-like gene of NOV11 are reported in Table N10. Variants are reported individually but any combination of all or a select subset of variants are also included. In summary, there are 4 variants reported.

10

Table N10. cSNP and Coding Variants for NOV11

Variant	Base Position of cSNP	Wild Type	Variant	Amino Acid Change
13374341	5008	G	T	silent
13374342	5012	A	G	Ile → Val at aa 1625
13376300	6808	C	T	silent
13376299	7323	C	T	silent

NOV12a SNP data

The DNA and protein sequences for the novel single nucleotide polymorphic variants of the Pancreatitis Associated Protein-like gene of NOV12a are reported in Table N11. Variants are reported individually but any combination of all or a select subset of variants are also included. In summary, there are 8 variants

20

Table N11. cSNP and Coding Variants for NOV12a

Variant	Base Position of cSNP	Wild Type	Variant	Amino Acid Change
13373957	68	T	C	silent
13373956	127	C	T	Ala → Val at aa 42
13373955	178	A	G	Asp → Gly at aa 59
13373954	182	A	G	silent
13373953	227	G	A	silent
13373952	314	C	T	silent
13373951	341	A	G	silent
13373950	441	A	G	Arg → Gly at aa 147

OTHER EMBODIMENTS

Although particular embodiments have been disclosed herein in detail, this has been done by way of example for purposes of illustration only, and is not intended to be limiting with respect to the scope of the appended claims, which follow. In particular, it is contemplated by the inventors that

5 various substitutions, alterations, and modifications may be made to the invention without departing from the spirit and scope of the invention as defined by the claims. The choice of nucleic acid starting material, clone of interest, or library type is believed to be a matter of routine for a person of ordinary skill in the art with knowledge of the embodiments described herein.

10 Other aspects, advantages, and modifications considered to be within the scope of the following claims.

WHAT IS CLAIMED IS:

1. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:
 - (a) a mature form of an amino acid sequence selected from the group consisting of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, and/or 38;
 - (b) a variant of a mature form of an amino acid sequence selected from the group consisting of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, and/or 38, wherein one or more amino acid residues in said variant differs from the amino acid sequence of said mature form, provided that said variant differs in no more than 15% of the amino acid residues from the amino acid sequence of said mature form;
 - (c) an amino acid sequence selected from the group consisting of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, and/or 38; and
 - (d) a variant of an amino acid sequence selected from the group consisting of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, and/or 38 wherein one or more amino acid residues in said variant differs from the amino acid sequence of said mature form, provided that said variant differs in no more than 15% of amino acid residues from said amino acid sequence.
2. The polypeptide of claim 1, wherein said polypeptide comprises the amino acid sequence of a naturally-occurring allelic variant of an amino acid sequence selected from the group consisting of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, and/or 38.
3. The polypeptide of claim 2, wherein said allelic variant comprises an amino acid sequence that is the translation of a nucleic acid sequence differing by a single nucleotide from a nucleic acid sequence selected from the group consisting of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and/or 37.

4. The polypeptide of claim 1, wherein the amino acid sequence of said variant comprises a conservative amino acid substitution.
5. An isolated nucleic acid molecule comprising a nucleic acid sequence encoding a polypeptide comprising an amino acid sequence selected from the group consisting of:
 - (a) a mature form of an amino acid sequence selected from the group consisting of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, and/or 38;
 - (b) a variant of a mature form of an amino acid sequence selected from the group consisting of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, and/or 38, wherein one or more amino acid residues in said variant differs from the amino acid sequence of said mature form, provided that said variant differs in no more than 15% of the amino acid residues from the amino acid sequence of said mature form;
 - (c) an amino acid sequence selected from the group consisting of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, and/or 38;
 - (d) a variant of an amino acid sequence selected from the group consisting of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, and/or 38, wherein one or more amino acid residues in said variant differs from the amino acid sequence of said mature form, provided that said variant differs in no more than 15% of amino acid residues from said amino acid sequence;
 - (e) a nucleic acid fragment encoding at least a portion of a polypeptide comprising an amino acid sequence chosen from the group consisting of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, and/or 38, or a variant of said polypeptide, wherein one or more amino acid residues in said variant differs from the amino acid sequence of said mature form, provided that said variant differs in no more than 15% of amino acid residues from said amino acid sequence; and
 - (f) a nucleic acid molecule comprising the complement of (a), (b), (c), (d) or (e).

6. The nucleic acid molecule of claim 5, wherein the nucleic acid molecule comprises the nucleotide sequence of a naturally-occurring allelic nucleic acid variant.
7. The nucleic acid molecule of claim 5, wherein the nucleic acid molecule encodes a polypeptide comprising the amino acid sequence of a naturally-occurring polypeptide variant.
8. The nucleic acid molecule of claim 5, wherein the nucleic acid molecule differs by a single nucleotide from a nucleic acid sequence selected from the group consisting of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and/or 37.
9. The nucleic acid molecule of claim 5, wherein said nucleic acid molecule comprises a nucleotide sequence selected from the group consisting of
 - (a) a nucleotide sequence selected from the group consisting of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and/or 37;
 - (b) a nucleotide sequence differing by one or more nucleotides from a nucleotide sequence selected from the group consisting of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and/or 37, provided that no more than 20% of the nucleotides differ from said nucleotide sequence;
 - (c) a nucleic acid fragment of (a); and
 - (d) a nucleic acid fragment of (b).
10. The nucleic acid molecule of claim 5, wherein said nucleic acid molecule hybridizes under stringent conditions to a nucleotide sequence chosen from the group consisting of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and/or 37, or a complement of said nucleotide sequence.
11. The nucleic acid molecule of claim 5, wherein the nucleic acid molecule comprises a nucleotide sequence selected from the group consisting of
 - (a) a first nucleotide sequence comprising a coding sequence differing by one or more nucleotide sequences from a coding sequence encoding said amino

- acid sequence, provided that no more than 20% of the nucleotides in the coding sequence in said first nucleotide sequence differ from said coding sequence;
- (b) an isolated second polynucleotide that is a complement of the first polynucleotide; and
 - (c) a nucleic acid fragment of (a) or (b).
12. A vector comprising the nucleic acid molecule of claim 11.
13. The vector of claim 12, further comprising a promoter operably-linked to said nucleic acid molecule.
14. A cell comprising the vector of claim 12.
15. An antibody that immunospecifically-binds to the polypeptide of claim 1.
16. The antibody of claim 15, wherein said antibody is a monoclonal antibody.
17. The antibody of claim 15, wherein the antibody is a humanized antibody.
18. A method for determining the presence or amount of the polypeptide of claim 1 in a sample, the method comprising:
- (a) providing the sample;
 - (b) contacting the sample with an antibody that binds immunospecifically to the polypeptide; and
 - (c) determining the presence or amount of antibody bound to said polypeptide, thereby determining the presence or amount of polypeptide in said sample.
19. A method for determining the presence or amount of the nucleic acid molecule of claim 5 in a sample, the method comprising:
- (a) providing the sample;
 - (b) contacting the sample with a probe that binds to said nucleic acid molecule; and
 - (c) determining the presence or amount of the probe bound to said nucleic acid molecule,

thereby determining the presence or amount of the nucleic acid molecule in said sample.

20. A method of identifying an agent that binds to a polypeptide of claim 1, the method comprising:
 - (a) contacting said polypeptide with said agent; and
 - (b) determining whether said agent binds to said polypeptide.
21. A method for identifying an agent that modulates the expression or activity of the polypeptide of claim 1, the method comprising:
 - (a) providing a cell expressing said polypeptide;
 - (b) contacting the cell with said agent; and
 - (c) determining whether the agent modulates expression or activity of said polypeptide,whereby an alteration in expression or activity of said peptide indicates said agent modulates expression or activity of said polypeptide.
22. A method for modulating the activity of the polypeptide of claim 1, the method comprising contacting a cell sample expressing the polypeptide of said claim with a compound that binds to said polypeptide in an amount sufficient to modulate the activity of the polypeptide.
23. A method of treating or preventing a NOVX-associated disorder, said method comprising administering to a subject in which such treatment or prevention is desired the polypeptide of claim 1 in an amount sufficient to treat or prevent said NOVX-associated disorder in said subject.
24. The method of claim 23, wherein said subject is a human.
25. A method of treating or preventing a NOVX-associated disorder, said method comprising administering to a subject in which such treatment or prevention is desired the nucleic acid of claim 5 in an amount sufficient to treat or prevent said NOVX-associated disorder in said subject.
26. The method of claim 25, wherein said subject is a human.

27. A method of treating or preventing a NOVX-associated disorder, said method comprising administering to a subject in which such treatment or prevention is desired the antibody of claim 15 in an amount sufficient to treat or prevent said NOVX-associated disorder in said subject.
28. The method of claim 27, wherein the subject is a human.
29. A pharmaceutical composition comprising the polypeptide of claim 1 and a pharmaceutically-acceptable carrier.
30. A pharmaceutical composition comprising the nucleic acid molecule of claim 5 and a pharmaceutically-acceptable carrier.
31. A pharmaceutical composition comprising the antibody of claim 15 and a pharmaceutically-acceptable carrier.
32. A kit comprising in one or more containers, the pharmaceutical composition of claim 29.
33. A kit comprising in one or more containers, the pharmaceutical composition of claim 30.
34. A kit comprising in one or more containers, the pharmaceutical composition of claim 31.
35. The use of a therapeutic in the manufacture of a medicament for treating a syndrome associated with a human disease, the disease selected from a NOVX-associated disorder, wherein said therapeutic is selected from the group consisting of a NOVX polypeptide, a NOVX nucleic acid, and a NOVX antibody.
36. A method for screening for a modulator of activity or of latency or predisposition to a NOVX-associated disorder, said method comprising:
 - (a) administering a test compound to a test animal at increased risk for a NOVX-associated disorder, wherein said test animal recombinantly expresses the polypeptide of claim 1;
 - (b) measuring the activity of said polypeptide in said test animal after administering the compound of step (a);

- (c) comparing the activity of said protein in said test animal with the activity of said polypeptide in a control animal not administered said polypeptide, wherein a change in the activity of said polypeptide in said test animal relative to said control animal indicates the test compound is a modulator of latency of or predisposition to a NOVX-associated disorder.
37. The method of claim 36, wherein said test animal is a recombinant test animal that expresses a test protein transgene or expresses said transgene under the control of a promoter at an increased level relative to a wild-type test animal, and wherein said promoter is not the native gene promoter of said transgene.
38. A method for determining the presence of or predisposition to a disease associated with altered levels of the polypeptide of claim 1 in a first mammalian subject, the method comprising:
- (a) measuring the level of expression of the polypeptide in a sample from the first mammalian subject; and
 - (b) comparing the amount of said polypeptide in the sample of step (a) to the amount of the polypeptide present in a control sample from a second mammalian subject known not to have, or not to be predisposed to, said disease,
- wherein an alteration in the expression level of the polypeptide in the first subject as compared to the control sample indicates the presence of or predisposition to said disease.
39. A method for determining the presence of or predisposition to a disease associated with altered levels of the nucleic acid molecule of claim 5 in a first mammalian subject, the method comprising:
- (a) measuring the amount of the nucleic acid in a sample from the first mammalian subject; and
 - (b) comparing the amount of said nucleic acid in the sample of step (a) to the amount of the nucleic acid present in a control sample from a second mammalian subject known not to have or not be predisposed to, the disease;

wherein an alteration in the level of the nucleic acid in the first subject as compared to the control sample indicates the presence of or predisposition to the disease.

40. A method of treating a pathological state in a mammal, the method comprising administering to the mammal a polypeptide in an amount that is sufficient to alleviate the pathological state, wherein the polypeptide is a polypeptide having an amino acid sequence at least 95% identical to a polypeptide comprising an amino acid sequence of at least one of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, and/or 38, or a biologically active fragment thereof.
41. A method of treating a pathological state in a mammal, the method comprising administering to the mammal the antibody of claim 15 in an amount sufficient to alleviate the pathological state.
42. An isolated nucleic acid molecule comprising SEQ ID NO:210, except that the nucleotide at position 887 is a nucleotide other than thymine, or the nucleotide at position 1144 is a nucleotide other than adenosine.
43. The nucleic acid molecule of claim 42, wherein the nucleotide at position 887 is other than thymine.
44. The nucleic acid molecule of claim 43, wherein the nucleotide at position 887 is cytosine.
45. An isolated nucleic acid molecule comprising SEQ ID NO:210, except that the nucleotide at position 1034 is a nucleotide other than cytosine, or the nucleotide at position 1244 is a nucleotide other than thymine.
46. The nucleic acid molecule of claim 45, wherein the nucleotide at position 1034 is other than cytosine.
47. The nucleic acid molecule of claim 46, wherein the nucleotide at position 1034 is thymine.

48. An isolated nucleic acid molecule comprising SEQ ID NO:210, except that the nucleotide at position 1223 is a nucleotide other than cytosine, or the nucleotide at position 1416 is a nucleotide other than adenine, or the nucleotide at position 1629 is other than thymine.
49. The nucleic acid molecule of claim 48, wherein the nucleotide at position 1223 is other than cytosine.
50. The nucleic acid molecule of claim 49, wherein the nucleotide at position 1223 is thymine.
51. An isolated nucleic acid molecule comprising SEQ ID NO:210, except that the nucleotide at position 832 is a nucleotide other than adenine, or the nucleotide at position 2003 is a nucleotide other than thymine.
52. The nucleic acid molecule of claim 51, wherein the nucleotide at position 832 is other than adenine.
53. The nucleic acid molecule of claim 52, wherein the nucleotide at position 832 is guanine.
54. A polypeptide comprising SEQ ID NO:211, except that the amino acid at position 325 is other than a glutamine.
55. The polypeptide of claim 54, wherein the amino acid at position 325 is leucine.
56. A polypeptide comprising SEQ ID NO:211, except that the amino acid at position 416 is other than asparagine, or the amino acid at position 487 is other than cysteine.
57. The polypeptide of claim 56, wherein the amino acid at position 416 is tyrosine.
58. A polypeptide comprising SEQ ID NO:211, except that the amino acid at position 221 is other than tyrosine.

59. The polypeptide of claim 58 wherein the amino acid at position 221 is cysteine.

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60/308,039 26 July 2001 (26.07.2001) US
60/311,266 9 August 2001 (09.08.2001) US(63) Related by continuation (CON) or continuation-in-part
(CIP) to earlier applications:US 60/262,959 (CIP)
Filed on 19 January 2001 (19.01.2001)
US 60/256,619 (CIP)
Filed on 19 December 2000 (19.12.2000)
US 60/272,408 (CIP)
Filed on 28 February 2001 (28.02.2001)
US 60/285,189 (CIP)
Filed on 20 April 2001 (20.04.2001)
US 60/308,039 (CIP)
Filed on 26 July 2001 (26.07.2001)
US 60/311,266 (CIP)
Filed on 9 August 2001 (09.08.2001)(71) Applicant (for all designated States except US): CURA-
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MA 02111 (US).(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
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GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
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Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent
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[Continued on next page]

(54) Title: HUMAN NUCLEIC ACIDS AND POLYPEPTIDES AND METHODS OF USE THEREOF

(57) Abstract: Disclosed are human polypeptides and nucleic acids encoding same. Also disclosed are vectors, host cells, antibodies and recombinant methods for producing the polypeptides and polynucleotides, as well as methods for using same.



WO 02/059315 A3



For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/50076

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 7	C12N15/12	C07K14/47	C07K14/705	C07K16/18	C07K16/28
	C12Q1/68	G01N33/50	G01N33/53	G01N33/68	A61K38/17
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According to International Patent Classification (IPC) or to both national classification and IPC					
B. FIELDS SEARCHED					
Minimum documentation searched (classification system followed by classification symbols)					
IPC 7 C07K G01N A61K					
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched					
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)					
BIOSIS, EMBL, MEDLINE, EPO-Internal, SEQUENCE SEARCH, WPI Data, PAJ					
C. DOCUMENTS CONSIDERED TO BE RELEVANT					
Category *	Citation of document, with indication, where appropriate, of the relevant passages				Relevant to claim No.
X	DATABASE EMBL [Online] standard; RNA; HUM; 7870 BP, 29 March 2000 (2000-03-29) POLITZ ET AL.: "Homo sapiens mRNA for stabilin-1 (stabl gene)" Database accession no. AJ275213 XP002231166 cited in the application the whole document --- -/--				1-41
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.					
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "Z" document member of the same patent family					
Date of the actual completion of the international search			Date of mailing of the international search report		
18 February 2003			15. 05. 2003		
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016			Authorized officer Kools, P		

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/50076

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE EMBL [Online] standard; RNA; HUM; 3260 BP, 12 July 2000 (2000-07-12) TAO Q ET AL.: "Homo sapiens CD44-like FELL mRNA, complete cds" Database accession no. AF160476 XP002231167 cited in the application the whole document	5,9-14, 42-59
X	--- DATABASE EMBL [Online] standard; RNA; HUM; 4575 BP, 29 September 2000 (2000-09-29) OHARA ET AL.: "Homo sapiens mRNA for FLJ00112 protein, partial cds" Database accession no. AK024503 XP002231168 the whole document	5,9-14
X	--- GOERDT S ET AL: "Identification of a novel high molecular weight protein preferentially expressed by sinusoidal endothelial cells in normal human tissues." THE JOURNAL OF CELL BIOLOGY, US, vol. 113, no. 6, June 1991 (1991-06), pages 1425-1437, XP008013836 ISSN: 0021-9525 the whole document	15-17
A	--- NAGASE T ET AL: "PREDICTION OF THE CODING SEQUENCES OF UNIDENTIFIED HUMAN GENES. XI. THE COMPLETE SEQUENCES OF 100 NEW CDNA CLONES FROM BRAIN WHICH CODE FOR LARGE PROTEINS IN VITRO" DNA RESEARCH, UNIVERSAL ACADEMY PRESS, JP, vol. 5, 1998, pages 277-286, XP000828191 ISSN: 1340-2838 the whole document	1-59
A	--- WO 00 39166 A (HUMAN GENOME SCIENCES INC ;LIAU GENE (US); TSIFRINA ELENA (US); AM) 6 July 2000 (2000-07-06) figures 1,4	1-41
A	--- DAY A J: "THE STRUCTURE AND REGULATION OF HYALURONAN-BINDING PROTEINS" BIOCHEMICAL SOCIETY TRANSACTIONS, COLCHESTER, ESSEX, GB, vol. 27, no. 2, 1999, pages 115-121, XP002926826 ISSN: 0300-5127 the whole document	1-41
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/50076

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 01 36638 A (LICHENSTEIN HENRI ;VERNET CORINE (US); CURAGEN CORP (US); FERNANDE) 25 May 2001 (2001-05-25) Nov 2, 3, 6, 7, 8, and 9, according to database sequences ---	5,9-14
P,X	WO 01 81544 A (WEIGEL PAUL A ;WEIGEL JANET A (US); ZHOU BIN (US)) 1 November 2001 (2001-11-01) Seq Id No 24 and 25 figure 33 ---	1-41
T	POLITZ OLIVER ET AL: "Stabilin-1 and -2 constitute a novel family of fasciclin-like hyaluronan receptor homologues." BIOCHEMICAL JOURNAL, vol. 362, no. 1, 2002, pages 155-164, XP002231164 15 February, 2002 ISSN: 0264-6021 the whole document ---	1-41
T	ADACHI HIDEKI ET AL: "FEEL-1, a novel scavenger receptor with in vitro bacteria-binding and angiogenesis-modulating activities." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 277, no. 37, 13 September 2002 (2002-09-13), pages 34264-34270, XP002231165 ISSN: 0021-9258 Published online on 19 June 2002 the whole document -----	1-41

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/50076

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-41 (partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 18, 19, and 36-39 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Although claims 23-28, 40, and 41 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: partially 1-41

Polypeptides with Seq ID No 2, or 4, variants thereof with no more than 15% amino acid differences. Polynucleotides with Seq ID No 1, or 3, or polynucleotides encoding said polypeptides, variants thereof with no more than 20% nucleotide differences, or fragments, or hybridizing to said polynucleotides. Vectors comprising said polynucleotides, host cells comprising said vectors. Antibodies which bind to said polypeptides. Methods of detecting the presence of said polypeptides or polynucleotides. Methods of identifying agents which bind to, or modulate the activity of said polypeptides. Methods of diagnosis and treatment of disorders having involvement of said polynucleotides or polypeptides. Pharmaceutical compositions or kits comprising said polypeptides, polynucleotides or antibodies.

2. Claims: partially 1-41

Polypeptides with Seq ID No 6 or 8, variants thereof with no more than 15% amino acid differences. Polynucleotides with Seq ID No 5, or 7, or polynucleotides encoding said polypeptides, variants thereof with no more than 20% nucleotide differences, or fragments, or hybridizing to said polynucleotides. Vectors comprising said polynucleotides, host cells comprising said vectors. Antibodies which bind to said polypeptides. Methods of detecting the presence of said polypeptides or polynucleotides. Methods of identifying agents which bind to, or modulate the activity of said polypeptides. Methods of diagnosis and treatment of disorders having involvement of said polynucleotides or polypeptides. Pharmaceutical compositions or kits comprising said polypeptides, polynucleotides or antibodies.

3. Claims: partially 1-41

Polypeptides with Seq ID No 10 or 12, variants thereof with no more than 15% amino acid differences. Polynucleotides with Seq ID No 9, or 11, or polynucleotides encoding said polypeptides, variants thereof with no more than 20% nucleotide differences, or fragments, or hybridizing to said polynucleotides. Vectors comprising said polynucleotides, host cells comprising said vectors. Antibodies which bind to said polypeptides. Methods of detecting the presence of said polypeptides or polynucleotides. Methods of identifying agents which bind to, or modulate the activity of said polypeptides. Methods of diagnosis and treatment of disorders having involvement of said polynucleotides or polypeptides. Pharmaceutical compositions or kits comprising said polypeptides, polynucleotides or antibodies.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

4. Claims: partially 1-41

Polypeptides with Seq ID No 14, variants thereof with no more than 15% amino acid differences. Polynucleotides with Seq ID No 13, or polynucleotides encoding said polypeptides, variants thereof with no more than 20% nucleotide differences, or fragments, or hybridizing to said polynucleotides. Vectors comprising said polynucleotides, host cells comprising said vectors. Antibodies which bind to said polypeptides. Methods of detecting the presence of said polypeptides or polynucleotides. Methods of identifying agents which bind to, or modulate the activity of said polypeptides. Methods of diagnosis and treatment of disorders having involvement of said polynucleotides or polypeptides. Pharmaceutical compositions or kits comprising said polypeptides, polynucleotides or antibodies.

5. Claims: partially 1-41

Polypeptides with Seq ID No 16, or 18, variants thereof with no more than 15% amino acid differences. Polynucleotides with Seq ID No 15, or 17, or polynucleotides encoding said polypeptides, variants thereof with no more than 20% nucleotide differences, or fragments, or hybridizing to said polynucleotides. Vectors comprising said polynucleotides, host cells comprising said vectors. Antibodies which bind to said polypeptides. Methods of detecting the presence of said polypeptides or polynucleotides. Methods of identifying agents which bind to, or modulate the activity of said polypeptides. Methods of diagnosis and treatment of disorders having involvement of said polynucleotides or polypeptides. Pharmaceutical compositions or kits comprising said polypeptides, polynucleotides or antibodies.

6. Claims: partially 1-41

Polypeptides with Seq ID No 20, variants thereof with no more than 15% amino acid differences. Polynucleotides with Seq ID No 19, or polynucleotides encoding said polypeptides, variants thereof with no more than 20% nucleotide differences, or fragments, or hybridizing to said polynucleotides. Vectors comprising said polynucleotides, host cells comprising said vectors. Antibodies which bind to said polypeptides. Methods of detecting the presence of said polypeptides or polynucleotides. Methods of identifying agents which bind to, or modulate the activity of said polypeptides. Methods of diagnosis and treatment of disorders having involvement of said polynucleotides or polypeptides. Pharmaceutical compositions or kits comprising said polypeptides, polynucleotides or antibodies.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

7. Claims: partially 1-41

Polypeptides with Seq ID No 22, or 24, or 26 variants thereof with no more than 15% amino acid differences. Polynucleotides with Seq ID No 21, or 23, or 25, or polynucleotides encoding said polypeptides, variants thereof with no more than 20% nucleotide differences, or fragments, or hybridizing to said polynucleotides. Vectors comprising said polynucleotides, host cells comprising said vectors. Antibodies which bind to said polypeptides. Methods of detecting the presence of said polypeptides or polynucleotides. Methods of identifying agents which bind to, or modulate the activity of said polypeptides. Methods of diagnosis and treatment of disorders having involvement of said polynucleotides or polypeptides. Pharmaceutical compositions or kits comprising said polypeptides, polynucleotides or antibodies.

8. Claims: partially 1-41

Polypeptides with Seq ID No 28, variants thereof with no more than 15% amino acid differences. Polynucleotides with Seq ID No 27, or polynucleotides encoding said polypeptides, variants thereof with no more than 20% nucleotide differences, or fragments, or hybridizing to said polynucleotides. Vectors comprising said polynucleotides, host cells comprising said vectors. Antibodies which bind to said polypeptides. Methods of detecting the presence of said polypeptides or polynucleotides. Methods of identifying agents which bind to, or modulate the activity of said polypeptides. Methods of diagnosis and treatment of disorders having involvement of said polynucleotides or polypeptides. Pharmaceutical compositions or kits comprising said polypeptides, polynucleotides or antibodies.

9. Claims: partially 1-41

Polypeptides with Seq ID No 30, variants thereof with no more than 15% amino acid differences. Polynucleotides with Seq ID No 29, or polynucleotides encoding said polypeptides, variants thereof with no more than 20% nucleotide differences, or fragments, or hybridizing to said polynucleotides. Vectors comprising said polynucleotides, host cells comprising said vectors. Antibodies which bind to said polypeptides. Methods of detecting the presence of said polypeptides or polynucleotides. Methods of identifying agents which bind to, or modulate the activity of said polypeptides. Methods of diagnosis and treatment of disorders having involvement of said polynucleotides or polypeptides. Pharmaceutical compositions or kits comprising said polypeptides, polynucleotides or antibodies.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

10. Claims: partially 1-41

Polypeptides with Seq ID No 32, or 34, variants thereof with no more than 15% amino acid differences. Polynucleotides with Seq ID No 31, or 33, or polynucleotides encoding said polypeptides, variants thereof with no more than 20% nucleotide differences, or fragments, or hybridizing to said polynucleotides. Vectors comprising said polynucleotides, host cells comprising said vectors. Antibodies which bind to said polypeptides. Methods of detecting the presence of said polypeptides or polynucleotides. Methods of identifying agents which bind to, or modulate the activity of said polypeptides. Methods of diagnosis and treatment of disorders having involvement of said polynucleotides or polypeptides. Pharmaceutical compositions or kits comprising said polypeptides, polynucleotides or antibodies.

11. Claims: partially 1-41

Polypeptides with Seq ID No 36, variants thereof with no more than 15% amino acid differences. Polynucleotides with Seq ID No 35, or polynucleotides encoding said polypeptides, variants thereof with no more than 20% nucleotide differences, or fragments, or hybridizing to said polynucleotides. Vectors comprising said polynucleotides, host cells comprising said vectors. Antibodies which bind to said polypeptides. Methods of detecting the presence of said polypeptides or polynucleotides. Methods of identifying agents which bind to, or modulate the activity of said polypeptides. Methods of diagnosis and treatment of disorders having involvement of said polynucleotides or polypeptides. Pharmaceutical compositions or kits comprising said polypeptides, polynucleotides or antibodies.

12. Claims: partially 1-41

Polypeptides with Seq ID No 38, variants thereof with no more than 15% amino acid differences. Polynucleotides with Seq ID No 37, or polynucleotides encoding said polypeptides, variants thereof with no more than 20% nucleotide differences, or fragments, or hybridizing to said polynucleotides. Vectors comprising said polynucleotides, host cells comprising said vectors. Antibodies binding to said polypeptides. Methods of detecting the presence of said polypeptides or polynucleotides. Methods of identifying agents which bind to, or modulate the activity of said polypeptides. Methods of diagnosis and treatment of disorders having involvement of said polynucleotides or polypeptides. Pharmaceutical compositions or kits comprising said polypeptides, polynucleotides or antibodies.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

13. Claims: 42-59 completely

Isolated polynucleotide comprising Seq ID No 210, with altered nucleotides at position 832, or 887, or 1034, or 1144, or 1223, or 1244, or 1416, or 1629, or 2003.

Polypeptide comprising Seq ID No 211, with different amino acid residues at position 211, or 325, or 416, or 487.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/50076

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0039166	A	06-07-2000	AU 2057800 A	31-07-2000
			CA 2357031 A1	06-07-2000
			EP 1141025 A1	10-10-2001
			WO 0039166 A1	06-07-2000

WO 0136638	A	25-05-2001	AU 1616801 A	30-05-2001
			CA 2391885 A1	25-05-2001
			EP 1232263 A2	21-08-2002
			WO 0136638 A2	25-05-2001
			AU 6229100 A	05-02-2001
			CA 2379925 A1	25-01-2001
			EP 1196576 A2	17-04-2002
			US 2002164699 A1	07-11-2002
			WO 0105971 A2	25-01-2001

WO 0181544	A	01-11-2001	AU 5380501 A	07-11-2001
			AU 5568801 A	07-11-2001
			CA 2407415 A1	01-11-2001
			EP 1282684 A2	12-02-2003
			EP 1278830 A2	29-01-2003
			WO 0180810 A2	01-11-2001
			WO 0181544 A2	01-11-2001
			US 2002197681 A1	26-12-2002

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